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Title:

Irrational differences in drug utilisation between men and women? A cross sectional analysis of all dispensed drugs in Sweden

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Abstract

Objectives: Differences between men and women are important to take into account when prescribing drugs. Since there is a lack of comprehensive overviews on sex- and gender differences in entire populations we analysed the prevalence and incidence of drug use in the Swedish population from a sex- and gender perspective.

Design: Cross sectional population database analysis

Methods: Data on all dispensed drugs in 2010 to the entire Swedish population (9 million inhabitants) were obtained from the Swedish Prescribed Drug Register. All pharmacological groups with ambulatory care prescribing accounting for >75% of the total volume in DDDs and a prevalence of >1% were included in the analysis. Crude and age adjusted difference in prevalence and incidence were calculated as risk ratios (RR) of women/men.

Results: A total of 2.8 million men and 3.6 million women, 60 percent of all men and 76 percent of all women in the country, purchased at least one prescribed drug during 2010. Women purchased more prescription drugs in all age groups except between 0 and 4 years. The largest sex difference in prevalence in absolute numbers was found for antibiotics that were more common in women, 265.5 treated patients (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (65.7 PAT/1000 women and 13.1 PAT/1000 men), and antidepressants (106.6 PAT/1000 women and 55.4 PAT/1000 men). Age adjusted relative sex differences in prevalence were found in 48 of the 50 identified pharmacological groups. The pharmacological groups with largest relative differences of dispensed drugs with higher use in women were antimycotics for systemic use (RR 6.6), drugs for osteoporosis (RR 4.9) and thyroid therapy (RR 4.5), while the use was higher in men for antigout preparations (RR 0.4), psychostimulants (0.6) and ACE-inhibitors (RR 0.7).

Conclusion: Substantial differences in drug utilisation between men and women were found. Some differences are both rational and desirable related to differences between the sexes in incidence or prevalence of disease or by biologic differences. Other differences are hard to explain on medical grounds and may indicate unequal treatment.

Introduction

Drug therapy plays an important role in restoring people's health and improving their quality of life. Consequently, drugs are the most important treatment options for most diseases and the majority of medical consultations result in a prescription.[1] Furthermore, pharmaceuticals also constitute a significant proportion of healthcare spending, more rapidly increasing than other healthcare components in many countries.[2,3] In Sweden, pharmaceuticals accounted for 12.6 % of the total health care expenditure in 2010[4] but the growth have been moderated after the implementation of major reforms.[5]

Rational drug use implies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community".[6] Individual requirements indicate that not only severity of disease, co-morbidity, renal function and age should be considered but also sex and gender. While it is evident that biological differences, commonly referred to as sex differences, should be considered when prescribing medicines, it is more disputable if it is rational to let socio-cultural differences, commonly referred to as gender differences, affect the prescription patterns. Sex- and gender differences in drug utilisation have been demonstrated in several therapeutic areas.[7-11] However, there is a lack of both comprehensive overviews on sex- and gender differences in entire populations and especially studies analysing the rational of the observed differences. Variations in morbidity may explain some differences whereas other differences may indicate inequities and under- or over use of certain drugs in men or women.

The aim of this study was to analyse the prevalence and incidence of drug use in the Swedish population from a sex- and gender perspective and to analyse the rationale of the observed differences.

Methods

This was a cross-sectional study analysing sex- and gender differences in prevalence and incidence of drug therapy in Sweden 2010, overall and within different pharmacological groups. Data were collected from the Swedish Prescribed Drug Register (SPDR) containing complete data (99.8 % coverage) with unique identifiers of all prescribed drugs dispensed to the entire Swedish population[12], 4 649 014 men and 4 691 668 women 31st December 2009.[13]

The period prevalence was defined as the proportion of the population in the country purchasing ≥1 prescription in 2010 and measured in number of patients per 1000 individuals (PAT/TIN). Incidence was defined as the proportion of the population redeeming their first prescription in 2010 after a one year wash-out period without any dispensation and it was measured in number of patients per 1000 person-years (PAT/1000 PYs).

Pharmacological groups included were selected by the procedure below:

1. All 89 Anatomical Therapeutic Chemical (ATC) 2nd level groups with drugs available on the Swedish market[14,15] were identified.
2. In large ATC groups and ATC groups with drugs used for multiple heterogeneous indications, i.e. cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06), ophthalmologicals (S01), a subdivision was done to ATC 3rd or 4th level to attain a more clinically relevant description of the utilisation.
3. ATC groups with less than 75% of the total sales volume in the country purchased on prescription (>25% of the total volume used in inpatient care and/or over-the-counter (OTC)) were excluded since sex distribution was not possible to collect for drugs used

as OTC or in inpatient care. Volume was measured in Defined Daily Doses (DDD), except for eight pharmacological groups for which there were no DDDs assigned.[15] For these groups packages were used as volume measure. The calculations of the proportion of the total volume that were purchased as prescriptions in ambulatory care were based on aggregated sales data from all Swedish pharmacies.

4. For the identified ATC groups at various hierarchical levels, groups that were purchased by less than 1% of the total Swedish population or used by less than 0.4% of men or women, respectively, were excluded to avoid random variation due to small numbers.

Statistics

Crude and age adjusted values were calculated. Age standardisation was made by direct standardisation, where the Swedish population on December 31st 2009 was used as a standard population. In the calculations, five-year age groups were used. Differences between the sexes were calculated as a risk ratio (RR) of women/men with 95% confidence intervals. All analyses were performed in Microsoft Office Excel 2007 and SAS ver. 9.2 (SAS Institute, Cary, NC) using descriptive statistical methods.

Results

In 2010, the total quantity of drugs sold in Sweden was 5.8 billion Defined Daily Doses (DDD), corresponding to 1 715 DDD/1000 inhabitants daily. The total expenditures were 35.6 billion Swedish Kronor (SEK) (100 SEK = 8.96 GBP, September 2012). The drugs sold by prescription in ambulatory care, and thus included in the study, accounted for 88 percent of the total volume and 72 percent of the total expenditures on drugs in the country.

A total of 2.8 million men and 3.6 million women, 60 percent of all men and 76 percent of all women in the country, purchased at least one prescribed drug during 2010. The proportion was highest among the elderly. Women purchased more prescription drugs in all age groups except among children under the age of 10, even if hormonal contraceptives were excluded (fig 1).

A total of 50 pharmacological (ATC) groups were included in the further analyses (fig 2). Crude sex differences in prevalence were found in 48 ATC groups (tab 1). After age adjustment, sex differences remained in 48 ATC groups. For antiglaucoma preparations (S01E) and endocrine therapy (L02) the sex difference disappeared after age adjustment while ARB (C09C+D) and calcium channel blockers (C08), where no difference were found before showed a slightly higher use in men after age adjustment. Beta blocking agents (C07) and cardiac glycosides (C01A) were more common in women before age adjustment but were found to be more common in men after. The large differences in drugs for treatment of bone diseases (M05), thyroid therapy (H03), mineral supplements (A12) and anti-dementia drugs (N06D) diminished after age adjustment even though the higher use in women remained (tab 1).

The pharmacological groups with largest relative differences with higher use in women were antimycotics for systemic use (RR 6.6), drugs for osteoporosis (RR 4.9) and thyroid therapy (RR 4.5), while the use was higher in men for antigout preparations (RR 0.4), psychostimulants (0.6) and ACE-inhibitors (RR 0.7) (fig 3).

The largest sex difference in absolute numbers was found for systemic antibacterials (J01) that were more common in women, 265.5 treated patients (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (H03), purchased by 65.7 PAT/1000 women and 13.1 PAT/1000 men, and antidepressants (N06A), purchased by 106.6 PAT/1000 women and 55.4 PAT/1000 men.

The incidence showed a similar pattern as the prevalence (tab 2). However, the sex differences were substantially higher for endocrine therapy (L02) and urinary antispasmodic agents (G04BD). Before age adjustment 40 pharmacological groups were more frequently dispensed to women and 8 to men while sex differences remained after age adjustment in 36 and 11 ATC-groups for women and men, respectively. In only one pharmacological group, drugs for treatment of bone diseases (M05), the sex difference diminished substantially after age adjustment.

Discussion

We found important sex differences in prescribed drugs dispensed to 2.8 million men and 3.6 million women that is the entire Swedish population. It is obvious that some of these differences may be explained by variations in disease prevalence, pathophysiology, diagnostics, treatment response and severity or by other biologic and societal differences such as those connected to the reproductive system.

However, it is evident that many discrepancies lack rational explanations.

Potential explainations to the higher drug utilisation in women could be that healthcare consultations are more frequent in women than in men.[16,17] In part this is explained by women's special needs during fertility and childbirth. Furthermore, studies have shown that women are more prone to seek preventive health care which also may explain the higher utilisation of certain drugs.[18,19] Also, it is more common for women to have chronic disabling diseases, such as rheumatic disease[20], and to have more co-morbidities requiring polypharmacy.[21] A higher proportion in the oldest age group is women and it is well known that drug utilisation is higher among the elderly[22,23] which could explain part of the differences. However, age adjustment only influenced a few of the ATC groups predominately used in the very old.

Some differences between the sexes were expected and rational. The higher use of antimycotics in women could be partly explained by gynecological infections such as vaginitis. Also, the 4.5 times higher use of thyroid therapy corresponds to a four times higher prevalence of impaired thyroid function in women.[24] Furthermore, the female dominance in utilisation of anti migraine drugs could also be explained by a two to three times higher prevalence of migraine among women than men.[25] Boys and men used more psychostimulants than women, corresponding well to a higher prevalence of ADHD[26] and autism in boys.[27]

Women were dispensed unproportional higher amounts of antibiotics than men. This is partly explained by the higher incidence of urinary tract infections (UTI) in women. However, gynaecological disease like vaginal prolapse can cause symptoms of UTI[28] and then operation rather than antibiotics would be the proper treatment. Furthermore, an overuse of antibiotic treatment could be due to inappropriate prescriptions for asymptomatic bacteriuria, commonly found in women.[29] Respiratory infections on the other hand have, at least in some studies, shown to be more common in men probably due to more smoking.[30] Based on this our interpretation is that there is an overuse of antibiotics in women.

Women were dispensed more antiobesity drugs than men in spite of obesity being more common in men.[31,32] Also, more women than men undergo obesity surgery.[33] There are reasons to believe that the socio cultural pressure for women to be slim is higher than for men explaining this prescription pattern.

In the cardiovascular field several differences in utilisation of prescribed drugs were found, one example being angiotensin-converting- enzyme (ACE) inhibitors which were more prescribed to men. ACE-inhibitors are primarily used for the treatment of heart failure and hypertension, both conditions with the same prevalence in both sexes. The difference might be due to that the adverse event coughing is more common in women.[34] Angiotensin Receptor Blockers (ARB) are the drugs often switched over when ACE-inhibitors are not tolerated and they also belong to the Renin-Angiotensin-Agent-System (RAAS) and are equally evidence based. Unexpectedly, ARB´s were prescribed to the same extent in men and women and we interpret this as an underuse of RAAS in women. Men purchased more lipid lowering agents than women and that is in line with the fact that secondary prevention studies show an underuse of lipid lowering drugs in women.[35-38] Reasons for this underuse could be that women suffer more from myalgia as an adverse reaction[39] but also that women are older and

have more co-morbidity when suffering from cardiovascular disease. The latter could lead to that doctors hesitate to prescribe intensive secondary preventive medication to women in spite of actual guidelines.

Older age in women could also explain gender difference in the use of anticoagulants. One of the most common indications is atrial fibrillation, a condition more commonly found in men but carrying a higher risk of fatal complications like embolic stroke, for women.[40] Underuse of anticoagulants in women with atrial fibrillation has been shown in earlier studies.[35,36,41-44] Men are also prescribed anti-arrhythmic drugs to a higher degree than women. This may be medically rational as women have a higher risk of the fatal arrhythmia "torsade de pointe-ventricular tachycardia" induced by some anti-arrhythmic agents like sotalol and quinidine.[45]

As shown in our study there are medically rational as well as irrational differences in drug utilisation between men and women. Whether these data from the whole of Sweden could be generalised to other countries is unknown. It is however plausible that the same international guidelines are used and that in some diseases/conditions the background is the same in other countries. As data on sex differences in drug utilisation from other countries are sparse, we are planning cross-national studies.

Healthcare professionals should aim to minimize inappropriate drug use in both genders. However, finding information about specific sex- and gender differences in pharmacokinetics and pharmacodynamics of different drugs can sometimes be both intricate and time consuming. Studies such like ours may help to raise awareness of irrational sex- and gender differences in drug utilisation and aid prescribers in their quest to provide a rational drug prescription. It is important to recognize that just providing data have a limited impact on

prescribing patterns.[46] A potential way forward may be to include recommendations in interactive decision support systems integrated in the medical record.[47]

Strengths and limitations

The main strength of this study is the complete coverage with all dispensed prescription drugs to the entire Swedish population. This provided a population-based overview of drug utilisation difficult to acquire in many other health systems. Furthermore, data on dispensed drugs is closer to the actual consumption than prescribed drugs and it is free from recall-bias common in patient reported data.

The most important limitation is the registry-based design including the uncertainty about sensitivity and specificity using dispensing data to assess actual patient consumption patterns. Furthermore, the Swedish Prescribed Drug Register lacks clinical information on diagnosis and off-label prescribing enabling more in-depth analyses on the rational behind the observed differences. Also, international generalisibility of the findings is unknown mainly because population based studies from other countries´ entire drug utilization are missing. We plan to perform such studies.

Conclusion

When analysing prevalence and incidence of dispensed drugs in the Swedish population medically unfounded differences between men and women are found. This is to our knowledge the first study of all dispensed drugs in an entire population of a country where not only the differences are reported but attempts to explain differences are made. While many differences seem well founded other rise questions of irrational use in one of the sexes. More research and awareness of the influence of sex- and gender in health

and disease are needed to ensure a rational and medically rational prescription to all men and women.

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Contributors: KSG proposed the study. All authors developed the study design. DL conducted the analyses. All authors contributed to interpreting the data and drafting the manuscript.

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Ethical approval: The study was approved by the regional Ethics Committee at Karolinska Institutet, Sweden. Dnr 2010/788-31/5.

Data sharing: Proposals for data sharing should be sent to the corresponding author.

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Figure 1. Proportions of the Swedish population purchasing at least one prescribed drug in 2010 by age and sex.

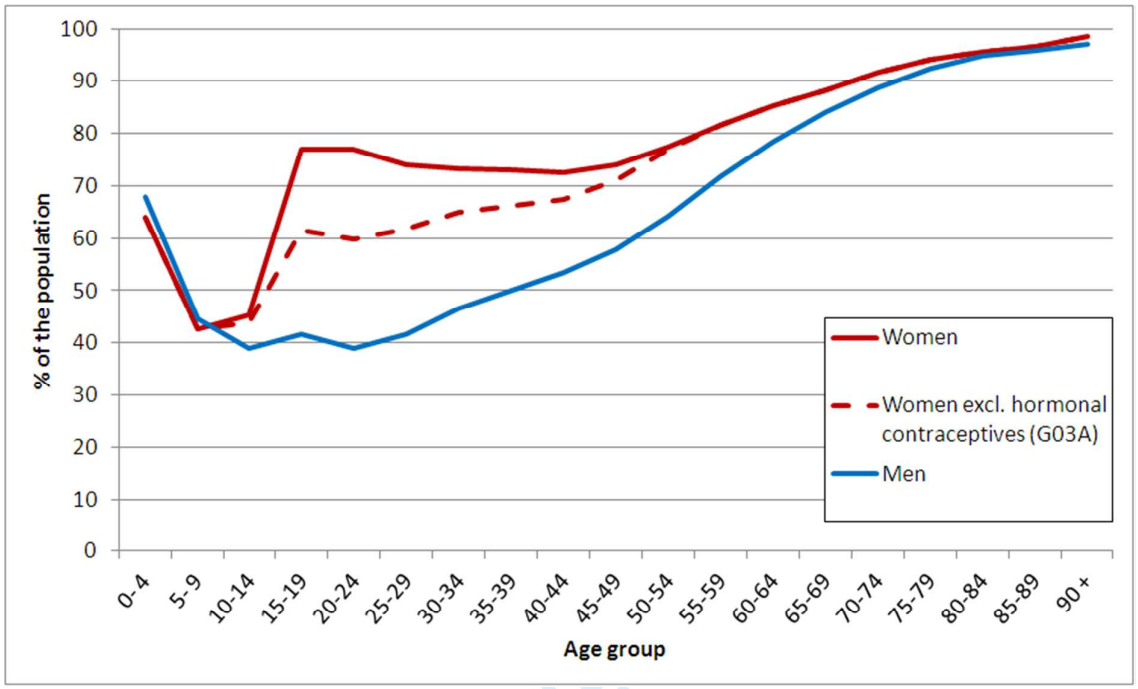
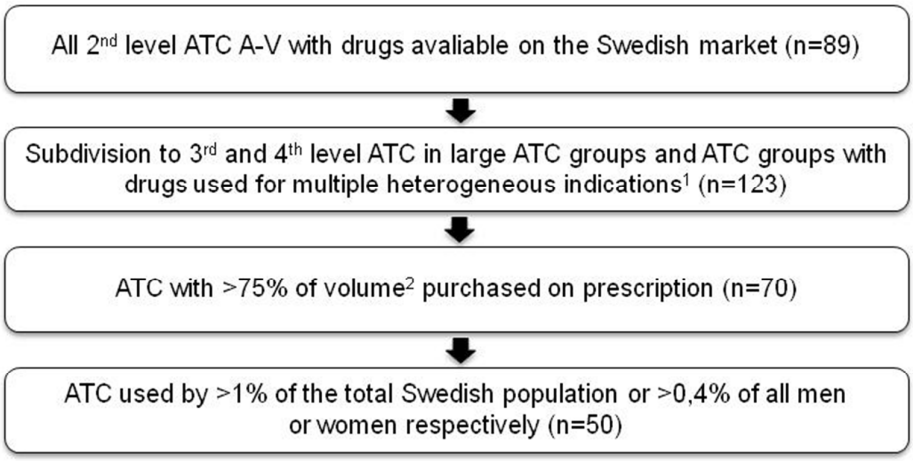


Figure 2. Flow chart showing the selection of pharmacological groups included in the specific analyses on sex- and gender differences in different therapeutic areas.



[1] Cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06) and ophthalmologicals (S01)

[2] Volume was measured in DDD, except for eight ATC groups without any assigned DDD values where packages were used instead.

Figure 3. Pharmacological groups with the highest age adjusted relative differences in prevalence 2010.

ATC	Pharmacological group	PAT/TIN	
		Men	Women
J02	Antimycotics for systemic use	2.8	18.9
M05	Drugs for treatment of bone diseases	3.2	19.3
H03	Thyroid therapy	13.1	65.7
N02C	Antimigraine preparations	5.0	17.2
A12	Mineral supplements	16.2	57.3
A08	Antiobesity preparations	1.6	4.1
J05	Antivirals for systemic use	7.9	14.8
P01	Antiprotozoals	11.0	20.6
N06A	Antidepressants	55.4	106.6
H01	Pituitary and hypothalamic hormones	2.5	4.1
C09C+D	Angiotensin II antagonists and comb.	45.2	46.6
C08	Calcium channel blockers	60.8	59.6
C01A	Cardiac glycosides	6.0	6.8
C10	Lipid modifying agents	98.0	81.1
C01D	Vasodilators used in cardiac diseases	24.9	23.6
B01	Antithrombotic agents	109.8	97.7
A10	Drugs used in diabetes	45.3	34.5
C09A+B	ACE inhibitors and combinations	78.1	60.9
N06B	Psychostimulants	6.9	4.1
M04	Antigout preparations	12.2	5.9

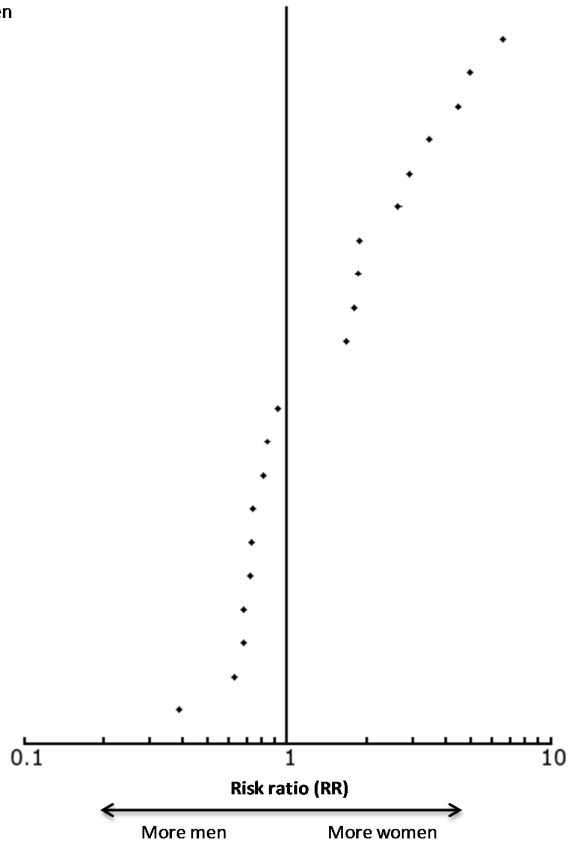


Table I. Sex differences in prevalence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups*. The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/TIN = number of patients (men or women) per 1000 individuals.

ATC	Pharmacological group	PAT/TIN		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.8	18.9	6.9 (6.7-7.0)	6.6 (6.4-6.7)
M05	Drugs for treatment of bone diseases	3.2	19.3	6.0 (5.9-6.1)	4.9 (4.9-5.0)
H03	Thyroid therapy	13.1	65.7	5.0 (5.0-5.0)	4.5 (4.4-4.5)
N02C	Antimigraine Preparations	5.0	17.2	3.4 (3.4-3.5)	3.4 (3.4-3.5)
A12	Mineral supplements	16.2	57.3	3.5 (3.5-3.6)	2.9 (2.9-2.9)
A08	Antiobesity preparations	1.6	4.1	2.6 (2.5-2.7)	2.6 (2.6-2.7)
J05	Antivirals for systemic use	7.9	14.8	1.9 (1.9-1.9)	1.9 (1.8-1.9)
P01	Antiprotozoals	11.0	20.6	1.9 (1.8-1.9)	1.8 (1.8-1.9)
N06A	Antidepressants	55.4	106.6	1.9 (1.9-1.9)	1.8 (1.8-1.8)
H01	Pituitary and hypothalamic hormones and analogues	2.5	4.1	1.7 (1.6-1.7)	1.7 (1.6-1.7)
N05B	Anxiolytics	39.4	70.0	1.8 (1.8-1.8)	1.6 (1.6-1.6)
N05C	Hypnotics and sedatives	58.4	103.8	1.8 (1.8-1.8)	1.6 (1.6-1.6)
M03	Muscle relaxants	6.4	10.0	1.6 (1.5-1.6)	1.5 (1.5-1.6)
B03	Antianemic preparations	40.4	73.2	1.8 (1.8-1.8)	1.5 (1.5-1.5)
J01	Antibacterials for systemic use	191.3	265.5	1.4 (1.4-1.4)	1.4 (1.4-1.4)
L04	Immunosuppressants	7.3	10.1	1.4 (1.3-1.4)	1.3 (1.3-1.4)
G04BD	Urinary antispasmodics	6.1	9.6	1.6 (1.5-1.6)	1.3 (1.3-1.3)
A02	Drugs for acid related disorders	70.1	101.9	1.5 (1.4-1.5)	1.3 (1.3-1.3)
H02	Corticosteroids for systemic use	37.2	52.0	1.4 (1.4-1.4)	1.3 (1.3-1.3)
S01B	Anti-inflammatory agents	12.7	19.0	1.5 (1.5-1.5)	1.3 (1.3-1.3)

A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	13.8	19.4	1.4 (1.4-1.4)	1.3 (1.3-1.3)
N02A	Opioids	66.9	93.0	1.4 (1.4-1.4)	1.3 (1.3-1.3)
C03	Diuretics	59.5	92.8	1.6 (1.6-1.6)	1.2 (1.2-1.2)
S02	Otologicals	4.5	5.7	1.3 (1.2-1.3)	1.2 (1.2-1.2)
R03	Drugs for obstructive airway diseases	71.8	88.8	1.2 (1.2-1.2)	1.2 (1.2-1.2)
S03	Ophthalmological and otological preparations	23.3	28.4	1.2 (1.2-1.2)	1.2 (1.2-1.2)
N03	Antiepileptics	18.2	22.1	1.2 (1.2-1.2)	1.1 (1.1-1.2)
N05A	Antipsychotics	13.6	16.5	1.2 (1.2-1.2)	1.1 (1.1-1.1)
N06D	Anti-dementia drugs	3.4	5.4	1.6 (1.6-1.6)	1.1 (1.1-1.1)
N04	Anti-parkinson drugs	6.8	8.5	1.2 (1.2-1.3)	1.1 (1.0-1.1)
S01E	Antiglaucoma preparations and miotics	13.6	18.5	1.4 (1.3-1.4)	1.0 (1.0-1.0)
L02	Endocrine therapy	6.3	7.6	1.2 (1.2-1.2)	1.0 (0.9-1.0)
C07	Beta blocking agents	97.8	107.6	1.1 (1.1-1.1)	0.9 (0.9-0.9)
C09C+D	Angiotensin II antagonists and combinations	45.2	46.6	1.0 (1.0-1.0)	0.9 (0.9-0.9)
C08	Calcium channel blockers	60.8	59.6	1.0 (1.0-1.0)	0.8 (0.8-0.8)
C01A	Cardiac glycosides	6.0	6.8	1.1 (1.1-1.2)	0.8 (0.8-0.8)
C10	Lipid modifying agents	98.0	81.1	0.8 (0.8-0.8)	0.7 (0.7-0.7)
C01D	Vasodilators used in cardiac diseases	24.9	23.6	0.9 (0.9-1.0)	0.7 (0.7-0.7)
B01	Antithrombotic agents	109.8	97.7	0.9 (0.9-0.9)	0.7 (0.7-0.7)
A10	Drugs used in diabetes	45.3	34.5	0.8 (0.8-0.8)	0.7 (0.7-0.7)
C09A+B	ACE-inhibitors and combinations	78.1	60.9	0.8 (0.8-0.8)	0.7 (0.7-0.7)
N06B	Psychostimulants	6.9	4.1	0.6 (0.6-0.6)	0.6 (0.6-0.6)
M04	Antigout preparations	12.2	5.9	0.5 (0.5-0.5)	0.4 (0.4-0.4)

*The following pharmacological groups are not presented in the table due to sex-specific indications; G02 Other gynecologicals (used by 9.8 PAT/1000 women and 0.2 PAT/1000 men), G03A Hormonal contraceptives (used by 132.1 PAT/1000 women and 0.1 PAT/1000 men), G03C Estrogens (used by 69.6 PAT/1000 women and 0.1 PAT/1000 men), G03D Progestogens (used by 15.9 PAT/1000 women and 0.0 PAT/1000 men), G03F Progestogens and estrogens in combination (used by 12.3 PAT/1000 women and 0.0 PAT/1000 men), G04C

Drugs used in benign prostatic hypertrophy (used by 0.3 PAT/1000 women and 26.2 PAT/1000 men) and G04BE Drugs used in erectile dysfunction (used by 25.4 PAT/1000 men and 0.1 PAT/1000 women).

Table II. Sex differences in incidence of drug therapy in Sweden 2010 by pharmacological group. Crude and age adjusted relative differences for included ATC groups*. The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/1000 PYs = number of patients (men or women) per 1000 patient-years.

ATC	Pharmacological group	PAT/1000 PYs		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.28	13.23	5.8 (5.7-5.9)	5.5 (5.4-5.6)
H03	Thyroid therapy	1.55	5.77	3.7 (3.6-3.8)	3.5 (3.4-3.6)
M05	Drugs for treatment of bone diseases	0.97	3.98	4.1 (4.0-4.2)	3.5 (3.4-3.6)
N02C	Antimigraine Preparations	1.89	4.99	2.6 (2.6-2.7)	2.7 (2.6-2.7)
A08	Antiobesity preparations	0.55	1.41	2.6 (2.5-2.7)	2.6 (2.5-2.7)
H01	Pituitary and hypothalamic hormones and analogues	0.99	2.45	2.5 (2.4-2.6)	2.5 (2.4-2.6)
A12	Mineral supplements	5.82	14.85	2.6 (2.5-2.6)	2.2 (2.2-2.2)
J05	Antivirals for systemic use	4.6	8.53	1.9 (1.8-1.9)	1.8 (1.8-1.8)
P01	Antiprotozoals	9.38	16.83	1.8 (1.8-1.8)	1.8 (1.8-1.8)
B03	Antianemic preparations	12.28	23.72	1.9 (1.9-2.0)	1.7 (1.7-1.7)
N06A	Antidepressants	15.35	24.71	1.6 (1.6-1.6)	1.5 (1.5-1.5)
L02	Endocrine therapy	1.37	2.43	1.8 (1.7-1.8)	1.5 (1.5-1.6)
N05B	Anxiolytics	17.9	28.41	1.6 (1.6-1.6)	1.5 (1.5-1.5)
M03	Muscle relaxants	4.5	6.67	1.5 (1.5-1.5)	1.5 (1.4-1.5)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	6.68	10.27	1.4 (1.4-1.4)	1.4 (1.4-1.4)
A02	Drugs for acid related disorders	25.47	37.35	1.5 (1.5-1.5)	1.4 (1.4-1.4)
N05C	Hypnotics and sedatives	18.9	26.94	1.4 (1.4-1.4)	1.3 (1.3-1.3)
S01B	Anti-inflammatory agents	9.27	13.71	1.5 (1.5-1.5)	1.3 (1.3-1.3)
H02	Corticosteroids for systemic use	21.36	28.28	1.3 (1.3-1.3)	1.3 (1.3-1.3)
N03	Antiepileptics	4.76	6.29	1.3 (1.3-1.3)	1.2 (1.2-1.3)

L04	Immunosuppressants	1.43	1.8	1.3 (1.2-1.3)	1.2 (1.2-1.3)
J01	Antibacterials for systemic use	126.14	153.73	1.2 (1.2-1.2)	1.2 (1.2-1.2)
R03	Drugs for obstructive airway diseases	27.19	32.11	1.2 (1.2-1.2)	1.2 (1.2-1.2)
N04	Anti-parkinson drugs	1.67	2.26	1.4 (1.3-1.4)	1.2 (1.2-1.2)
S02	Otologicals	3.39	4.04	1.2 (1.2-1.2)	1.2 (1.1-1.2)
N02A	Opioids	39.55	48.3	1.2 (1.2-1.2)	1.1 (1.1-1.2)
C03	Diuretics	10.63	14.35	1.3 (1.3-1.4)	1.1 (1.1-1.2)
S03	Ophthalmological and otological preparations	18.43	21.41	1.2 (1.2-1.2)	1.1 (1.1-1.1)
G04BD	Urinary antispasmodics	2.63	3.33	1.3 (1.2-1.3)	1.1 (1.1-1.1)
N05A	Antipsychotics	3.27	4.03	1.2 (1.2-1.3)	1.1 (1.1-1.1)
N06D	Anti-dementia drugs	0.91	1.38	1.5 (1.5-1.6)	1.1 (1.0-1.1)
B01	Antithrombotic agents	15.05	17.48	1.2. (1.1-1.2)	1.0 (1.0-1.1)
C07	Beta blocking agents	12.16	13.61	1.1 (1.1-1.1)	1.0 (1.0-1.0)
S01E	Antiglaucoma preparations and miotics	1.9	2.15	1.1 (1.1-1.2)	1.0 (0.9-1.0)
C09C+D	Angiotensin II antagonists and combinations	6.18	6.42	1.0 (1.0-1.1)	0.9 (0.9-1.0)
C08	Calcium channel blockers	10.35	10.72	1.0 (1.0-1.0)	0.9 (0.9-0.9)
C01A	Cardiac glycosides	1.09	1.24	1.1 (1.1-1.2)	0.9 (0.8-0.9)
C09A+B	ACE-inhibitors and combinations	14.28	13.11	0.9 (0.9-0.9)	0.8 (0.8-0.8)
C10	Lipid modifying agents	13.01	11.28	0.9 (0.9-0.9)	0.8 (0.8-0.8)
A10	Drugs used in diabetes	4.83	3.79	0.8 (0.8-0.8)	0.7 (0.7-0.7)
N06B	Psychostimulants	2.36	1.57	0.7 (0.6-0.7)	0.7 (0.7-0.7)
C01D	Vasodilators used in cardiac diseases	8.34	6.93	0.8 (0.8-0.8)	0.7 (0.7-0.7)
M04	Antigout preparations	2.71	1.44	0.5 (0.5-0.5)	0.4 (0.4-0.5)

*The following pharmacological groups were excluded from the table due to sex-specific indications; G02 Other gynecologicals (used by 5.33 PAT/1000 PYs among women and 0.03 PAT/1000 PYs among men), G03A Hormonal contraceptives (used by 42.09 PAT/1000 PYs among women and 0.04 PAT/1000 PYs among men), G03C Estrogens (used by 16.44 PAT/1000 PYs among women and 0.03 PAT/1000 PYs among men), G03D Progestogens (used by 11.20 PAT/1000 PYs among women and 0.01 PAT/1000 PYs among men), G03F

Progestogens and estrogens in combination (used by 2.56 PAT/1000 PYs among women and 0.00 PAT/1000 PYs among men), G04C Drugs used in benign prostatic hypertrophy (used by 0.20 PAT/1000 PYs among women and 7.34 PAT/1000 PYs among men) and G04BE Drugs used in erectile dysfunction (used by 0.03 PAT/1000 PYs among women and 10.16 PAT/1000 PYs among men).

Article Summary

Article focus'

To analyse the pharmaceutical drug use in a whole country

To make a sex- and gender analysis

To analyse reasons behind irrational drug use

'Key messages'

- Differences in drug utilisation between men and women in both prevalence and incidence were found in Sweden overall, and for 48 of 50 pharmacological groups.
- Many sex differences in drug use in our study may be explained by sex differences in morbidity or biology. Other differences are hard to explain on medical grounds and may indicate unequal treatment.
- There are few studies analysing the rationale of the observed sex differences.

Strengths and limitations of this study

Registry-based design include uncertainty about sensitivity and specificity using dispensing data to assess actual patient consumption patterns. The Swedish Prescribed Drug Register lacks clinical information on diagnosis and off-label prescribing and thus un-enabling more in-depth analyses. Also, international generalisibility of the findings is unknown mainly because population based studies from other countries´ entire drug utilization are missing.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	na

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	na
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	na
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	na
		Cross-sectional study—Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ open

Differences in drug utilisation between men and women - a cross sectional analysis of all dispensed drugs in Sweden

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Title:

Differences in drug utilisation between men and women - a cross sectional analysis of all dispensed drugs in Sweden

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Abstract

Objectives: Differences between men and women are important to take into account when prescribing drugs. There is a lack of comprehensive overviews on sex differences in drug utilisation. Therefore, we analysed the prevalence and incidence of drug use in all Swedish men and women.

Design: Cross-sectional population database analysis

Methods: Data on all dispensed drugs in 2010 to the entire Swedish population (9.3 million inhabitants) were obtained from the Swedish Prescribed Drug Register. All pharmacological groups with ambulatory care prescribing accounting for >75% of the total volume in Defined Daily Doses (DDDs) and a prevalence of >1% were included in the analysis. Crude and age adjusted difference in prevalence and incidence were calculated as risk ratios (RR) of women/men.

Results: In all, 2.8 million men (59%) and 3.6 million women (76%), purchased at least one prescribed drug during 2010. Women purchased more prescription drugs in all age groups except among children under the age of 10. The largest sex difference in prevalence in absolute numbers was found for antibiotics that were more common in women, 265.5 patients (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (65.7 PAT/1000 women and 13.1 PAT/1000 men), and antidepressants (106.6 PAT/1000 women and 55.4 PAT/1000 men). Age adjusted relative sex differences in prevalence were found in 48 of the 50 identified pharmacological groups. The pharmacological groups with the largest relative differences of dispensed drugs with higher use in women were antimycotics for systemic use (RR 6.6 CI 6.4-6.7), drugs for osteoporosis (RR 4.9 CI 4.9-5.0) and thyroid therapy (RR 4.5 CI 4.4-4.5), while in men the use was higher

for antigout agents(RR 0.4 CI 0.4-0.4), psychostimulants (RR 0.6 CI 0.6-0.6) and ACE inhibitors (angiotensin-converting-enzyme inhibitors) (RR 0.7 CI 0.7-0.7).

Conclusion: Substantial differences in drug utilisation between men and women were found. Some differences may be rational and desirable related to differences between the sexes in incidence or prevalence of disease or by biologic differences. Other differences are more difficult to explain on medical grounds and may indicate unequal treatment.

Introduction

Drug therapy plays an important role in preserving people's health and improving their quality of life. Consequently, drugs are the most important treatment options for most diseases and the majority of medical consultations result in a prescription.[1] Furthermore, pharmaceuticals also constitute a significant proportion of healthcare spending, more rapidly increasing than other healthcare components in many countries.[2 3] In Sweden, pharmaceuticals accounted for 12.6 % of the total health care expenditure in 2010,[4] but the growth has been moderated after the implementation of major reforms.[5]

Rational drug use implies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community".[6] Individual requirements indicate that not only severity of disease, co-morbidity, renal function and age should be considered, but also sex and gender. While it is evident that biological differences, commonly referred to as "sex differences", should be considered when prescribing medicines, it is unclear to what extent socio-cultural differences, commonly referred to as "gender differences" should be considered by the prescribing physician. Sex differences in drug utilisation have been demonstrated in several therapeutic areas.[7-11] However, there is a lack of both comprehensive overviews on sex- and gender differences of drug utilisation in entire populations and especially studies analysing the rationale of the observed differences. Variations in morbidity may explain some differences, whereas other differences may indicate inequities and under- or overuse of certain drugs in men or women.

The aim of this study was to analyse differences in prevalence and incidence of drug utilisation among men and women in the Swedish population and problematise the observed differences.

Methods

This was a cross-sectional study analysing sex differences in prevalence and incidence of drug use in ambulatory care in Sweden 2010, overall and within different pharmacological groups. Data were collected from the Swedish Prescribed Drug Register (SPDR), which contains complete data (>99 % coverage) with unique identifiers of all prescribed drugs (irrespective of reimbursement) dispensed to the entire Swedish population of 9.3 million inhabitants.[12,13]

The period prevalence was defined as the proportion of the population in the country purchasing ≥1 prescription in 2010 and measured in number of patients exposed per 1000 inhabitants (PAT/TIN). Incidence was defined as the proportion of the population redeeming their first prescription in 2010 after a one-year wash-out period with no dispensation and was measured in number of patients per 1000 person-years (PAT/1000 PYs).

Pharmacological groups were selected by using the following procedure:

1. All 89 Anatomical Therapeutic Chemical (ATC) 2nd level groups with drugs available on the Swedish market[14,15] were identified.
2. In large ATC groups and ATC groups with drugs used for multiple heterogeneous indications, i.e. cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06), ophthalmologicals (S01), a subdivision was done to ATC 3rd or 4th level to attain a more clinically relevant description of the utilisation.
3. ATC groups with less than 75% of the total sales volume in the country purchased on prescription were excluded since sex distribution was not possible to collect for those

purchased over-the-counter (OTC) or used in inpatient care. Volume was measured in Defined Daily Doses (DDDs), except for eight pharmacological groups for which there were no DDDs assigned.[15] For these groups, packages were used as volume measure. Calculations of the proportion of the total volume purchased as prescriptions in ambulatory care were based on aggregated sales data from all Swedish pharmacies.

4. For the identified ATC groups at various hierarchical levels, groups that were purchased by less than 1% of the total Swedish population or used by less than 0.4% of men or women, respectively, were excluded to avoid random variation due to small numbers.

Crude and age adjusted values were calculated. Age standardisation was performed by direct standardisation, where the Swedish population on 31 December 2009 (4 649 014 men and 4 691 668 women[13]) was used as the standard population. In the calculations, 5-year age groups were used. Differences between the sexes were calculated as a risk ratio (RR) of women/men with 95% confidence intervals (CI). All analyses were performed in Microsoft Excel 2007 and SAS ver. 9.2 (SAS Institute, Cary, NC) using descriptive statistical methods.

Results

In 2010, the total volume of drugs sold in Sweden was 5.8 billion Defined Daily Doses (DDD), corresponding to 1715 DDD/1000 inhabitants daily. The total expenditures were 35.6 billion Swedish Kronor (SEK) (100 SEK = 8.96 GBP, September 2012). Drugs prescribed in ambulatory care, and thus included in the study, accounted for 88 % of the total volume and 72 % of the total expenditures on drugs in the country.

In all, 2.8 million men (59%) and 3.6 million women (76%), purchased at least one prescribed drug during 2010. The older the patient, the higher the likelihood of drug purchase. Women purchased more prescription drugs in all age groups except among children under the age of 10, even when hormonal contraceptives were excluded (Figure 1).

Crude sex differences in prevalence were found in 48 of the 50 pharmacological ATC groups included (Figure 2, Table 1). After age adjustment, sex differences remained in 48 ATC groups. For antiglaucoma (S01E) and endocrine drugs (L02), the sex differences disappeared after age adjustment, while the opposite was seen for ARBs (angiotensin II receptor blockers) (C09C+D) and calcium channel blockers (C08), with a slightly higher use in men after age adjustment. Beta blocking agents (C07) and cardiac glycosides (C01A) were more common in women before age adjustment, but were found to be more common in men after adjustment. The large differences in drugs for treatment of bone diseases (M05), thyroid therapy (H03), mineral supplements (A12) and anti-dementia drugs (N06D) diminished after age adjustment, even though the higher use in women remained (Table 1).

The pharmacological groups with the largest relative differences with higher use in women were antimycotics for systemic use (RR 6.6), drugs for osteoporosis (RR 4.9) and thyroid therapy (RR 4.5), while the use was higher in men for antigout preparations (RR 0.4), psychostimulants (0.6) and ACE-inhibitors (RR 0.7) (Figure 3).

The largest sex difference in absolute numbers was found for systemic antibacterials (J01) that were more common in women, 265.5 patients exposed (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (H03), purchased by 65.7

PAT/1000 women and 13.1 PAT/1000 men, and antidepressants (N06A), purchased by 106.6 PAT/1000 women and 55.4 PAT/1000 men.

The incidence showed a similar pattern as the prevalence (Table 2). However, the sex differences were substantially higher for endocrine therapy (L02) and urinary antispasmodic agents (G04BD). Before age adjustment, 40 pharmacological groups were more frequently dispensed to women and eight groups to men. After age adjustment, sex differences remained in 36 and 11 ATC-groups for women and men, respectively. In only one pharmacological group, drugs for treatment of bone diseases (M05), the sex difference diminished substantially after age adjustment.

Discussion

This drug utilisation study shows substantial sex differences in the Swedish population. It is obvious that some of these differences may be explained by variations in disease prevalence, severity of disease, pathophysiology, diagnostics and treatment response or by other biologic differences such as those induced by pregnancy and/or lactation. However, it is also evident that other differences lack a rational medical explanation.

Throughout their lifespan, women have more contact with the health care system, which provides them with an extra opportunity for detection of disease. In the pre-menopausal years, a woman's need for contraceptives, pregnancy and childbirth and, in the peri- and postmenopausal period, screening programs for breast and cervical cancers and gynecological disorders require health care consultations.[16] Also, chronic disabling diseases associated with a chronic need for medication, such as musculoskeletal disorders, are more common in women

than men.[17] From a gender perspective, studies have shown that men are less prone to seek preventive health care.[18]

Some differences between the sexes were expected. The higher use of antimycotics in women could partly be explained by gynecological infections such as vaginitis. Also, the 4.5 times higher use of thyroid therapy corresponds to a four times higher prevalence of impaired thyroid function in women.[19] The sex difference in utilisation of anti migraine drugs could be explained by a two to three times higher prevalence of migraine among women.[20] Men used more psychostimulants, corresponding well to a higher prevalence of ADHD[21] and autism[22].

A large sex difference was observed for antibiotics. Men are more susceptible to infections than women in general, yet we found a higher absolute use of antibiotics in women. A common reason for prescribing antibiotics in primary care is urinary tract infection (UTI), which is much more prevalent in women.[23] An overdiagnosis of this condition in women has, however, been reported, which could potentially explain some of the higher use in women.[24]Women were dispensed more anti-obesity drugs than men in spite of obesity being more common in men.[25 26] Also, more women than men undergo obesity surgery.[27] There are reasons to believe that the sociocultural pressure for women to be slim is higher than for men which could explain this prescription pattern.

In the cardiovascular field several differences in utilisation of prescribed drugs were found. ACE inhibitors, primarily used for the treatment of heart failure and hypertension with the same prevalence in both sexes, were more used in men. This may be due to the higher frequency of coughing as an adverse event in women.[28] However, the alternative treatment ARB was dispensed to the same extent in both sexes. Our findings may therefor indicate an

under-use of renin-angiotensin-agents in women. Lipid lowering drugs were also used more often in men. The higher use may be explained by the higher prevalence of ischemic heart disease (IHD). However, studies have shown that these drugs are under-used for secondary prevention in women[29-32]. Reasons for this could be that women suffer more from myalgia as an adverse reaction[33] but also that women are older and have more co-morbidity when suffering from cardiovascular disease, thus receiving less intensive secondary preventive medication.

Men used more anticoagulants. The most common indication for anticoagulants is atrial fibrillation, a condition more commonly found in men but carrying a higher risk of fatal complications like embolic stroke, for women.[34] Underuse of anticoagulants in women with atrial fibrillation has been shown in earlier studies.[29 32 35-38] Men are also prescribed anti-arrhythmic drugs to a higher degree than women. This may be appropriate as women have a higher risk of the fatal arrhythmia "torsade de pointe-ventricular tachycardia" induced by some anti-arrhythmics like sotalol and quinidine.[39]

The main strength of this study is the complete coverage of all dispensed prescription drugs to the entire Swedish population. This provides a population-based overview of drug utilisation difficult to acquire in many other health systems. Furthermore, data on dispensed drugs is closer to the actual consumption than data on prescribed drugs, and it is free from recall bias common in patient reported data.[40]

The most important limitation is the lack of information on patient characteristics and clinical data to assess the rationale behind the observed differences. Furthermore, it is important to emphasize that gender differences may only be hypothesised from these data.

In conclusion, in this large study we found substantial differences in drug utilisation between men and women. In an attempt to explain these sex differences we searched the literature. Some sex disparities could be explained by differences in prevalence of disease or frequency of adverse reactions. Less medically justified explanations were also identified such as overestimation of risk vs. benefit in women compared to men. We also found suggestions that gender aspects such as societal acceptance of overweight in women compared to men may be involved. More research and a greater awareness of the influence of sex- and gender in health and disease are needed to ensure rational drug use in both men and women.

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Contributors: KSG proposed the study. All authors developed the study design. DL conducted the analyses. All authors contributed to interpreting the data and drafting the manuscript.

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Ethical approval: The study was approved by the regional Ethics Committee at Karolinska Institutet, Sweden. Ref. no. 2010/788-31/5.

Data sharing: Proposals for data sharing should be sent to the corresponding author.

Figure 1. Proportions of the Swedish population purchasing at least one prescribed drug in 2010 by age and sex.

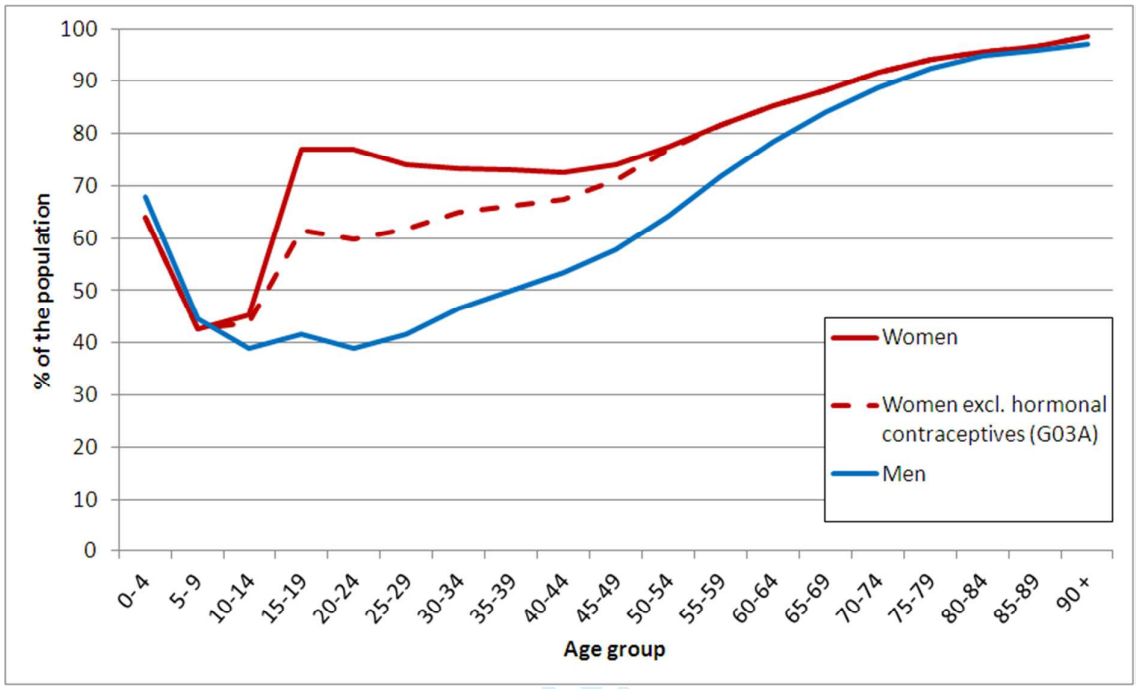
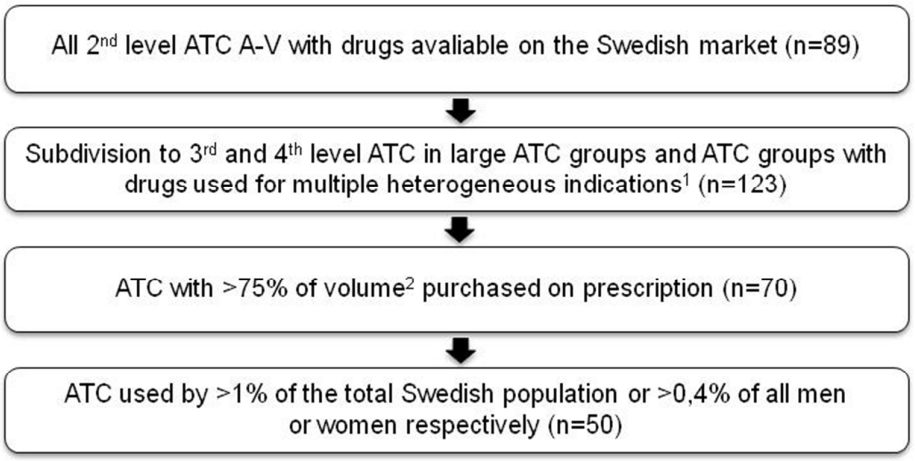


Figure 2. Flow chart showing the selection of pharmacological groups included in the specific analyses on sex- and gender differences in different therapeutic areas.



[1] Cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06) and ophthalmologicals (S01)

[2] Volume was measured in Defined Daily Doses (DDDs), except for eight ATC groups without any assigned DDD values where packages were used instead.

Figure 3. Pharmacological groups with the highest age adjusted relative differences in prevalence 2010.

ATC	Pharmacological group	PAT/TIN	
		Men	Women
J02	Antimycotics for systemic use	2.8	18.9
M05	Drugs for treatment of bone diseases	3.2	19.3
H03	Thyroid therapy	13.1	65.7
N02C	Antimigraine preparations	5.0	17.2
A12	Mineral supplements	16.2	57.3
A08	Antiobesity preparations	1.6	4.1
J05	Antivirals for systemic use	7.9	14.8
P01	Antiprotozoals	11.0	20.6
N06A	Antidepressants	55.4	106.6
H01	Pituitary and hypothalamic hormones	2.5	4.1
C09C+D	Angiotensin II antagonists and comb.	45.2	46.6
C08	Calcium channel blockers	60.8	59.6
C01A	Cardiac glycosides	6.0	6.8
C10	Lipid modifying agents	98.0	81.1
C01D	Vasodilators used in cardiac diseases	24.9	23.6
B01	Antithrombotic agents	109.8	97.7
A10	Drugs used in diabetes	45.3	34.5
C09A+B	ACE inhibitors and combinations	78.1	60.9
N06B	Psychostimulants	6.9	4.1
M04	Antigout preparations	12.2	5.9

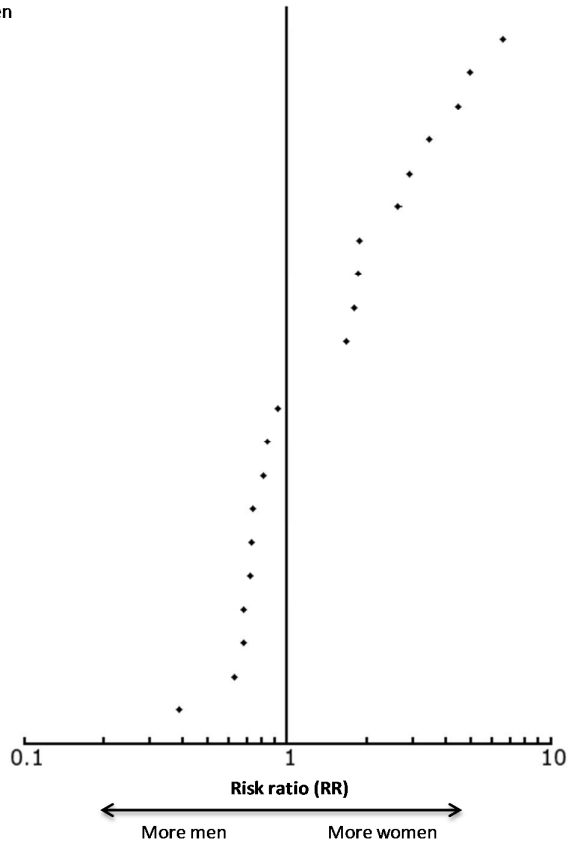


Table I. Sex differences in prevalence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/TIN = number of patients (men or women) per 1000 individuals. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/TIN		RR (95 C.I.)	Age adj (95 C.
		Men	Women	Women/Men	Women/
J02	Antimycotics for systemic use	2.75	18.90	6.87 (6.74-7.00)	6.56 (6.4
M05	Drugs for treatment of bone diseases	3.19	19.28	6.04 (5.94-6.14)	4.95 (4.8
H03	Thyroid therapy	13.12	65.67	5.00 (4.96-5.05)	4.46 (4.4
N02C	Antimigraine Preparations	5.03	17.24	3.43 (3.38-3.48)	3.44 (3.3
A12	Mineral supplements	16.19	57.29	3.54 (3.51-3.57)	2.90 (2.8
A08	Antiobesity preparations	1.59	4.13	2.60 (2.53-2.67)	2.62 (2.5
J05	Antivirals for systemic use	7.85	14.79	1.88 (1.86-1.91)	1.86 (1.8
P01	Antiprotozoals	11.00	20.55	1.87 (1.85-1.89)	1.85 (1.8
N06A	Antidepressants	55.35	106.60	1.93 (1.92-1.93)	1.79 (1.7
H01	Pituitary and hypothalamic hormones and analogues	2.46	4.08	1.66 (1.62-1.70)	1.66 (1.6
N05B	Anxiolytics	39.39	70.01	1.78 (1.77-1.79)	1.60 (1.5
N05C	Hypnotics and sedatives	58.35	103.83	1.78 (1.77-1.79)	1.56 (1.5
M03	Muscle relaxants	6.38	9.98	1.56 (1.54-1.59)	1.53 (1.5
B03	Antianemic preparations	40.35	73.24	1.82 (1.81-1.83)	1.48 (1.4
J01	Antibacterials for systemic use	191.26	265.58	1.39 (1.39-1.39)	1.36 (1.3
L04	Immunosuppressants	7.32	10.05	1.37 (1.35-1.39)	1.33 (1.3
G04BD	Urinary antispasmodics	6.12	9.61	1.57 (1.55-1.60)	1.33 (1.3
A02	Drugs for acid related disorders	70.08	101.87	1.45 (1.45-1.46)	1.31 (1.3
H02	Corticosteroids for systemic use	37.17	51.98	1.40 (1.39-1.41)	1.30 (1.3
S01B	Anti-inflammatory agents	12.72	18.95	1.49 (1.47-1.50)	1.30 (1.2
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	13.77	19.35	1.40 (1.39-1.42)	1.29 (1.2
N02A	Opioids	66.90	92.97	1.39 (1.38-1.40)	1.27 (1.2
C03	Diuretics	59.48	92.83	1.56 (1.55-1.57)	1.24 (1.2
S02	Otologicals	4.54	5.71	1.26 (1.24-1.28)	1.23 (1.2
R03	Drugs for obstructive airway diseases	71.79	88.80	1.24 (1.23-1.24)	1.20 (1.2
S03	Ophthalmological and otological preparations	23.31	28.38	1.22 (1.21-1.23)	1.18 (1.1
N03	Antiepileptics	18.22	22.08	1.21 (1.20-1.22)	1.15 (1.1

N05A	Antipsychotics	13.59	16.51	1.21 (1.20-1.23)	1.11 (1.0
N06D	Anti-dementia drugs	3.38	5.41	1.60 (1.57-1.63)	1.10 (1.0
N04	Anti-parkinson drugs	6.83	8.49	1.24 (1.22-1.26)	1.06 (1.0
S01E	Antiglaucoma preparations and miotics	13.57	18.49	1.36 (1.35-1.38)	1.02 (1.0
L02	Endocrine therapy	6.34	7.60	1.20 (1.18-1.22)	0.96 (0.9
C07	Beta blocking agents	97.82	107.57	1.10 (1.10-1.10)	0.94 (0.9
C09C+D	Angiotensin II antagonists and combinations	45.16	46.56	1.03 (1.02-1.04)	0.91 (0.9
C08	Calcium channel blockers	60.84	59.61	0.98 (0.97-0.98)	0.84 (0.8
C01A	Cardiac glycosides	6.01	6.83	1.14 (1.12-1.16)	0.81 (0.7
C10	Lipid modifying agents	98.03	81.05	0.83 (0.82-0.83)	0.74 (0.7
C01D	Vasodilators used in cardiac diseases	24.94	23.61	0.95 (0.94-0.95)	0.73 (0.7
B01	Antithrombotic agents	109.81	97.68	0.89 (0.89-0.89)	0.72 (0.7
A10	Drugs used in diabetes	45.27	34.48	0.76 (0.76-0.77)	0.68 (0.6
C09A+B	ACE-inhibitors and combinations	78.14	60.90	0.78 (0.78-0.78)	0.68 (0.6
N06B	Psychostimulants	6.94	4.11	0.59 (0.58-0.60)	0.62 (0.6
M04	Antigout preparations	12.24	5.91	0.48 (0.48-0.49)	0.38 (0.3

*The following pharmacological groups are not presented in the table due to sex-specific indications; G02 Other gynecologicals (used by 9.79 PAT/1000 women and 0.20 PAT/1000 men), G03A Hormonal contraceptives (used by 132.05 PAT/1000 women and 0.08 PAT/1000 men), G03C Estrogens (used by 69.62 PAT/1000 women and 0.08 PAT/1000 men), G03D Progestogens (used by 15.90 PAT/1000 women and 0.03 PAT/1000 men), G03F Progestogens and estrogens in combination (used by 12.26 PAT/1000 women and 0.00 PAT/1000 men), G04C Drugs used in benign prostatic hypertrophy (used by 0.25 PAT/1000 women and 26.23 PAT/1000 men) and G04BE Drugs used in erectile dysfunction (used by 25.38 PAT/1000 men and 0.07 PAT/1000 women).

Table II. Sex differences in incidence of drug therapy in Sweden 2010 by pharmacological group. Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/1000 PYs = number of patients (men or women) per 1000 patient-years. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/1000 PYs		RR (95 C.I.)	Age adj (95 C.
		Men	Women	Women/Men	Women/
J02	Antimycotics for systemic use	2.28	13.23	5.80 (5.68-5.92)	5.49 (5.3
H03	Thyroid therapy	1.55	5.77	3.72 (3.62-3.81)	3.49 (3.4
M05	Drugs for treatment of bone diseases	0.97	3.98	4.11 (3.98-4.24)	3.49 (3.3
N02C	Antimigraine Preparations	1.89	4.99	2.64 (2.57-2.70)	2.67 (2.6
A08	Antiobesity preparations	0.55	1.41	2.57 (2.45-2.69)	2.60 (2.4
H01	Pituitary and hypothalamic hormones and analogues	0.99	2.45	2.47 (2.38-2.55)	2.48 (2.4
A12	Mineral supplements	5.82	14.85	2.55 (2.52-2.59)	2.21 (2.1
J05	Antivirals for systemic use	4.60	8.53	1.85 (1.82-1.89)	1.80 (1.7
P01	Antiprotozoals	9.38	16.83	1.80 (1.77-1.82)	1.79 (1.7
B03	Antianemic preparations	12.28	23.72	1.93 (1.91-1.95)	1.70 (1.6
N06A	Antidepressants	15.35	24.71	1.61 (1.59-1.62)	1.52 (1.5
L02	Endocrine therapy	1.37	2.43	1.78 (1.73-1.84)	1.52 (1.4
N05B	Anxiolytics	17.90	28.41	1.59 (1.57-1.60)	1.47 (1.4
M03	Muscle relaxants	4.50	6.67	1.48 (1.46-1.51)	1.46 (1.4
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	6.68	10.27	1.39 (1.37-1.41)	1.39 (1.3
A02	Drugs for acid related disorders	25.47	37.35	1.47 (1.46-1.48)	1.38 (1.3
N05C	Hypnotics and sedatives	18.90	26.94	1.43 (1.41-1.44)	1.32 (1.3
S01B	Anti-inflammatory agents	9.27	13.71	1.48 (1.46-1.50)	1.29 (1.2
H02	Corticosteroids for systemic use	21.36	28.28	1.32 (1.31-1.33)	1.27 (1.2
N03	Antiepileptics	4.76	6.29	1.32 (1.30-1.35)	1.25 (1.2
L04	Immunosuppressants	1.43	1.80	1.26 (1.22-1.30)	1.23 (1.2
J01	Antibacterials for systemic use	126.14	153.73	1.22 (1.21-1.22)	1.21 (1.2
R03	Drugs for obstructive airway diseases	27.19	32.11	1.18 (1.17-1.19)	1.19 (1.1
N04	Anti-parkinson drugs	1.67	2.26	1.35 (1.31-1.39)	1.19 (1.1
S02	Otologicals	3.39	4.04	1.19 (1.17-1.22)	1.17 (1.1
N02A	Opioids	39.55	48.30	1.22 (1.21-1.23)	1.14 (1.1
C03	Diuretics	10.63	14.35	1.35 (1.33-1.37)	1.14 (1.1
S03	Ophthalmological and otological preparations	18.43	21.41	1.16 (1.15-1.17)	1.14 (1.1

G04BD	Urinary antispasmodics	2.63	3.33	1.27 (1.24-1.30)	1.10 (1.0
N05A	Antipsychotics	3.27	4.03	1.23 (1.21-1.26)	1.07 (1.0
N06D	Anti-dementia drugs	0.91	1.38	1.52 (1.46-1.58)	1.07 (1.0
B01	Antithrombotic agents	15.05	17.48	1.16. (1.15-1.7)	1.05 (1.0
C07	Beta blocking agents	12.16	13.61	1.12 (1.11-1.13)	1.02 (1.0
S01E	Antiglaucoma preparations and miotics	1.90	2.15	1.13 (1.10-1.16)	0.96 (0.9
C09C+D	Angiotensin II antagonists and combinations	6.18	6.42	1.04 (1.02-1.05)	0.95 (0.9
C08	Calcium channel blockers	10.35	10.72	1.04 (1.02-1.05)	0.93 (0.9
C01A	Cardiac glycosides	1.09	1.24	1.14 (1.10-1.18)	0.86 (0.8
C09A+B	ACE-inhibitors and combinations	14.28	13.11	0.92 (0.91-0.93)	0.83 (0.8
C10	Lipid modifying agents	13.01	11.28	0.87 (0.86-0.88)	0.81 (0.8
A10	Drugs used in diabetes	4.83	3.79	0.79 (0.77-0.80)	0.73 (0.7
N06B	Psychostimulants	2.36	1.57	0.67 (0.65-0.69)	0.70 (0.6
C01D	Vasodilators used in cardiac diseases	8.34	6.93	0.83 (0.82-0.84)	0.69 (0.6
M04	Antigout preparations	2.71	1.44	0.53 (0.51-0.55)	0.44 (0.4

*The following pharmacological groups were excluded from the table due to sex-specific indications; G02 Other gynecologicals (used by 5.33 PAT/1000 PYs among women and 0.03 PAT/1000 PYs among men), G03A Hormonal contraceptives (used by 42.09 PAT/1000 PYs among women and 0.04 PAT/1000 PYs among men), G03C Estrogens (used by 16.44 PAT/1000 PYs among women and 0.03 PAT/1000 PYs among men), G03D Progestogens (used by 11.20 PAT/1000 PYs among women and 0.01 PAT/1000 PYs among men), G03F Progestogens and estrogens in combination (used by 2.56 PAT/1000 PYs among women and 0.00 PAT/1000 PYs among men), G04C Drugs used in benign prostatic hypertrophy (used by 0.20 PAT/1000 PYs among women and 7.34 PAT/1000 PYs among men) and G04BE Drugs used in erectile dysfunction (used by 0.03 PAT/1000 PYs among women and 10.16 PAT/1000 PYs among men).

Article Summary

Article focus

- To analyse drug utilisation in a whole country
- To identify areas of potential discrepancies in drug use patterns between men and women
- To review existing literature for explanations for differences in drug use between men and women
- To raise awareness for drug use differences between men and women which may not be rational

Key messages'

- Differences in drug utilisation between men and women in both prevalence and incidence were found in Sweden overall, and for 48 of 50 pharmacological groups.
- Many sex differences in drug use in our study may be explained by sex differences in morbidity or biology. Other differences are hard to explain on medical grounds and may indicate unequal treatment.
- There are few studies analysing the rational of the observed sex differences.

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Title:

~~Irrational differences~~Differences in drug utilisation between men and women~~? A~~ - a cross sectional analysis of all dispensed drugs in Sweden

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Abstract

Objectives: Differences between men and women are important to take into account when prescribing drugs. ~~Since there~~There is a lack of comprehensive overviews on sex~~- and gender~~ differences in ~~entire populations~~drug utilisation. Therefore, we analysed the prevalence and incidence of drug use in ~~the~~all Swedish ~~population from a sex- and gender perspective.~~men and women.

Design: Cross~~-~~-sectional population database analysis

Methods: Data on all dispensed drugs in 2010 to the entire Swedish population (9.3 million inhabitants) were obtained from the Swedish Prescribed Drug Register. All pharmacological groups with ambulatory care prescribing accounting for >75% of the total volume in Defined Daily Doses (DDDs) and a prevalence of >1% were included in the analysis. Crude and age adjusted difference in prevalence and incidence were calculated as risk ratios (RR) of women/men.

Results: ~~A total of~~In all, 2.8 million men (59%) and 3.6 million women~~, 60 percent of all men and~~ (76~~ percent of all women in the country,~~%), purchased at least one prescribed drug during 2010. Women purchased more prescription drugs in all age groups except ~~between 0 and 4 years~~among children under the age of 10. The largest sex difference in prevalence in absolute numbers was found for antibiotics that were more common in women, 265.5 ~~treated~~ patients (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (65.7 PAT/1000 women and 13.1 PAT/1000 men), and antidepressants (106.6 PAT/1000 women and 55.4 PAT/1000 men). Age adjusted relative sex differences in prevalence were found in 48 of the 50 identified pharmacological groups. The pharmacological groups with the largest relative differences of dispensed drugs with higher use in women were antimycotics for systemic use (RR 6.6 CI 6.4-6.7), drugs for osteoporosis

(RR 4.9 CI 4.9-5.0) and thyroid therapy (RR 4.5 CI 4.4-4.5), while in men the use was higher ~~in men~~ for antigout ~~preparations~~ agents(RR 0.4 CI 0.4-0.4), psychostimulants (RR 0.6 CI 0.6-0.6) and ACE- inhibitors (~~RR 0~~angiotensin-converting-enzyme inhibitors) (RR 0.7 CI 0.7-0.7).

Conclusion: Substantial differences in drug utilisation between men and women were found. Some differences ~~are both~~may be rational and desirable related to differences between the sexes in incidence or prevalence of disease or by biologic differences. Other differences are ~~hard~~more difficult to explain on medical grounds and may indicate unequal treatment.

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Introduction

Drug therapy plays an important role in ~~restoring~~preserving people's health and improving their quality of life. Consequently, drugs are the most important treatment options for most diseases and the majority of medical consultations result in a prescription.[1] Furthermore, pharmaceuticals also constitute a significant proportion of healthcare spending, more rapidly increasing than other healthcare components in many countries.[2 3] In Sweden, pharmaceuticals accounted for 12.6 % of the total health care expenditure in 2010,[4] but the growth ~~have~~has been moderated after the implementation of major reforms.[5]

Rational drug use implies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and ~~their~~the community".[6] Individual requirements indicate that not only severity of disease, co-morbidity, renal function and age should be considered, but also sex and gender. While it is evident that biological differences, commonly referred to as "sex differences~~;~~", should be considered when prescribing medicines, it is ~~more disputable if it is rational~~unclear to ~~let~~what extent socio-cultural differences, commonly referred to as "gender differences~~;~~" ~~affect~~ should be considered by the ~~the prescription patterns.~~prescribing physician. Sex~~- and gender~~ differences in drug utilisation have been demonstrated in several therapeutic areas.[7-11] However, there is a lack of both comprehensive overviews on sex- and gender differences of drug utilisation in entire populations and especially studies analysing the ~~rational~~rationale of the observed differences. Variations in morbidity may explain some differences, whereas other differences may indicate inequities and under- or ~~over use~~overuse of certain drugs in men or women.

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The aim of this study was to analyse ~~the~~ differences in prevalence and incidence of drug ~~use~~utilisation among men and women in the Swedish population ~~from a sex- and gender perspective~~ and ~~to analyse the rationale of~~problematise the observed differences.

Methods

This was a cross-sectional study analysing sex~~- and gender~~ differences in prevalence and incidence of drug ~~therapy~~use in ambulatory care in Sweden 2010, overall and within different pharmacological groups. Data were collected from the Swedish Prescribed Drug Register (SPDR~~) containing~~), which contains complete data (>99 % coverage) with unique identifiers of all prescribed drugs (irrespective of reimbursement) dispensed to the entire Swedish population of 9.3 million inhabitants.[12]~~, 4 649 014 men and 4 691 668 women 31st December 2009.~~[13]

The period prevalence was defined as the proportion of the population in the country purchasing ≥1 prescription in 2010 and measured in number of patients exposed per 1000 ~~individuals~~inhabitants (PAT/TIN). Incidence was defined as the proportion of the population redeeming their first prescription in 2010 after a one-year wash-out period ~~without any~~with no dispensation and ~~it~~ was measured in number of patients per 1000 person-years (PAT/1000 PYs).

Pharmacological groups ~~included~~ were selected by using the following procedure ~~below~~:

1. All 89 Anatomical Therapeutic Chemical (ATC) 2nd level groups with drugs available on the Swedish market[14 15] were identified.

2. In large ATC groups and ATC groups with drugs used for multiple heterogeneous indications, i.e. cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06), ophthalmologicals (S01), a subdivision was done to ATC 3rd or 4th level to attain a more clinically relevant description of the utilisation.
3. ATC groups with less than 75% of the total sales volume in the country purchased on prescription ~~(>25% of the total volume used in inpatient care and/or over the counter (OTC))~~ were excluded since sex distribution was not possible to collect for ~~drugs used as~~ those purchased over-the-counter (OTC) or used in inpatient care. Volume was measured in Defined Daily Doses (~~DDD~~DDDs), except for eight pharmacological groups for which there were no DDDs assigned.[15] For these groups, packages were used as volume measure. ~~The calculations~~ Calculations of the proportion of the total volume ~~that were~~ purchased as prescriptions in ambulatory care were based on aggregated sales data from all Swedish pharmacies.
4. For the identified ATC groups at various hierarchical levels, groups that were purchased by less than 1% of the total Swedish population or used by less than 0.4% of men or women, respectively, were excluded to avoid random variation due to small numbers.

Crude and age adjusted values were calculated. Age standardisation was ~~made~~performed by direct standardisation, where the Swedish population on 31 December ~~31st~~ 2009 (4 649 014 men and 4 691 668 women[13]) was used as ~~a~~the standard population. In the calculations, ~~five~~5-year age groups were used. Differences between the sexes were calculated as a risk ratio (RR) of women/men with 95% confidence intervals~~.~~ (CI). All analyses were performed in

Microsoft ~~Office~~ Excel 2007 and SAS ver. 9.2 (SAS Institute, Cary, NC) using descriptive statistical methods.

Results

In 2010, the total ~~quantity~~volume of drugs sold in Sweden was 5.8 billion Defined Daily Doses (DDD), corresponding to ~~1 715~~1715 DDD/1000 inhabitants daily. The total expenditures were 35.6 billion Swedish Kronor (SEK) (100 SEK = 8.96 GBP, September 2012). ~~The drugs sold by prescription~~Drugs prescribed in ambulatory care, and thus included in the study, accounted for 88 ~~percent~~% of the total volume and 72 ~~percent~~% of the total expenditures on drugs in the country.

~~A total of~~In all, 2.8 million men (59%) and 3.6 million women~~, 60 percent of all men and~~ (76 ~~percent of all women in the country,~~%), purchased at least one prescribed drug during 2010. The ~~proportion was highest among~~older the patient, the ~~elderly~~higher the likelihood of drug purchase. Women purchased more prescription drugs in all age groups except among children under the age of 10, even ~~if~~when hormonal contraceptives were excluded (~~fig~~Figure 1).

~~A total of 50 pharmacological (ATC) groups were included in the further analyses (fig 2).~~ Crude sex differences in prevalence were found in 48 of the 50 pharmacological ATC groups ~~(tab~~included (Figure 2, Table 1). After age adjustment, sex differences remained in 48 ATC groups. For antiglaucoma ~~preparations~~ (S01E) and endocrine ~~therapy~~drugs (L02~~)~~), the sex ~~difference~~differences disappeared after age adjustment, while ~~ARB~~the opposite was seen for ARBs (angiotensin II receptor blockers) (C09C+D) and calcium channel blockers (C08), ~~where no difference were found before showed~~with a slightly higher use in men after age

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adjustment. Beta blocking agents (C07) and cardiac glycosides (C01A) were more common in women before age adjustment, but were found to be more common in men after adjustment. The large differences in drugs for treatment of bone diseases (M05), thyroid therapy (H03), mineral supplements (A12) and anti-dementia drugs (N06D) diminished after age adjustment, even though the higher use in women remained (~~tab~~Table 1).

The pharmacological groups with the largest relative differences with higher use in women were antimycotics for systemic use (RR 6.6), drugs for osteoporosis (RR 4.9) and thyroid therapy (RR 4.5), while the use was higher in men for antigout preparations (RR 0.4), psychostimulants (0.6) and ACE-inhibitors (RR 0.7) (~~fig~~Figure 3).

The largest sex difference in absolute numbers was found for systemic antibacterials (J01) that were more common in women, 265.5 ~~treated~~ patients exposed (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (H03), purchased by 65.7 PAT/1000 women and 13.1 PAT/1000 men, and antidepressants (N06A), purchased by 106.6 PAT/1000 women and 55.4 PAT/1000 men.

The incidence showed a similar pattern as the prevalence (~~tab~~Table 2). However, the sex differences were substantially higher for endocrine therapy (L02) and urinary antispasmodic agents (G04BD). Before age adjustment, 40 pharmacological groups were more frequently dispensed to women and ~~8~~eight groups to men ~~while~~. After age adjustment, sex differences remained ~~after age adjustment~~ in 36 and 11 ATC-groups for women and men, respectively. In only one pharmacological group, drugs for treatment of bone diseases (M05), the sex difference diminished substantially after age adjustment.

Discussion

~~We found important~~This drug utilisation study shows substantial sex differences in ~~prescribed drugs dispensed to 2.8 million men and 3.6 million women that is~~ the ~~entire~~ Swedish population. It is obvious that some of these differences may be explained by variations in disease prevalence, severity of disease, pathophysiology, diagnostics~~,~~ and treatment response ~~and severity~~ or by other biologic ~~and societal~~ differences such as those ~~connected to the reproductive system~~induced by pregnancy and/or lactation. However, it is also evident that other differences lack a rational medical explanation.

~~However, it is evident that many discrepancies lack rational explanations.~~

~~Potential explanations to the higher drug utilisation in women could be that healthcare consultations are more frequent in women than in men.[16 17] In part this is explained by women's special needs during fertility and childbirth. Furthermore, studies have shown that women are more prone to seek preventive health care which also may explain the higher utilisation of certain drugs.[18 19] Also, it is more common for women to have chronic disabling diseases, such as rheumatic disease~~

Throughout their lifespan, women have more contact with the health care system, which provides them with an extra opportunity for detection of disease. In the pre-menopausal years, a woman's need for contraceptives, pregnancy and childbirth and, in the peri- and postmenopausal period, screening programs for breast and cervical cancers and gynecological disorders require health care consultations.[16] Also, chronic disabling diseases associated with a chronic need for medication, such as musculoskeletal disorders, are more common in women than men.[17] From a gender perspective, studies have shown that men are less prone to seek preventive health care.[~~20~~18]

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Some differences between the sexes were expected. The higher use of antimycotics in women could partly be explained by gynecological infections such as vaginitis. Also, the 4.5 times higher use of thyroid therapy corresponds to a four times higher prevalence of impaired thyroid function in women.[19], ~~and to have more co-morbidities requiring polypharmacy.~~ The sex difference in utilisation of anti migraine drugs could be explained by a two to three times higher prevalence of migraine among women.[21,20] ~~A higher proportion in the oldest age group is women and it is well known that drug utilisation is higher among the elderly,[22,23] which could explain part of the differences. However, age adjustment only influenced a few of the ATC groups predominately used in the very old.~~

~~Some differences between the sexes were expected and rational. The higher use of antimycotics in women could be partly explained by gynecological infections such as vaginitis. Also, the 4.5 times higher use of thyroid therapy corresponds to a four times higher prevalence of impaired thyroid function in women.~~ Men used more psychostimulants, corresponding well to a higher prevalence of ADHD[21] and autism.[24,22] ~~Furthermore, the female dominance in utilisation of anti migraine drugs could also be explained by a two to three times higher prevalence of migraine among women than men.~~

A large sex difference was observed for antibiotics. Men are more susceptible to infections than women in general, yet we found a higher absolute use of antibiotics in women. A common reason for prescribing antibiotics in primary care is urinary tract infection (UTI), which is much more prevalent in women.[25,23] ~~Boys and men used more psychostimulants than women, corresponding well to a higher prevalence of ADHD.~~ An overdiagnosis of this condition in women has, however, been reported, which could potentially explain some of the higher use in women,[26,24] ~~and autism in boys.~~[27]

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~~Women were dispensed unproportional higher amounts of antibiotics than men. This is partly explained by the higher incidence of urinary tract infections (UTI) in women. However, gynaecological disease like vaginal prolapse can cause symptoms of UTI[28] and then operation rather than antibiotics would be the proper treatment. Furthermore, an overuse of antibiotic treatment could be due to inappropriate prescriptions for asymptomatic bacteriuria, commonly found in women.[29] Respiratory infections on the other hand have, at least in some studies, shown to be more common in men probably due to more smoking.[30] Based on this our interpretation is that there is an overuse of antibiotics in women.~~

Women were dispensed more anti-obesity drugs than men in spite of obesity being more common in men.[~~31~~25 ~~32~~26] Also, more women than men undergo obesity surgery.[~~33~~27] There are reasons to believe that the ~~socio-cultural~~sociocultural pressure for women to be slim is higher than for men ~~explaining~~ which could explain this prescription pattern.

In the cardiovascular field several differences in utilisation of prescribed drugs were found~~, one example being angiotensin-converting-enzyme (~~, ACE~~)~~ inhibitors ~~which were more prescribed to men. ACE inhibitors are~~, primarily used for the treatment of heart failure and hypertension~~, both conditions~~ with the same prevalence in both sexes~~. The difference might~~, were more used in men. This may be due to ~~that~~ the higher frequency of coughing as an adverse event ~~coughing is more common in~~ in women.[~~34~~28] ~~Angiotensin Receptor Blockers (ARB) are~~ However, the ~~drugs often switched over when ACE-inhibitors are not tolerated and they also belong to the Renin-Angiotensin-Agent-System (RAAS) and are equally evidence based. Unexpectedly, ARB´s were prescribed~~alternative treatment ARB was dispensed to the same extent in ~~men and women and we interpret this as~~both sexes. Our findings may therefor indicate an ~~underuse~~under-use of ~~RAAS~~ renin-angiotensin-agents in women. ~~Men purchased more lipid~~Lipid lowering ~~agents than~~

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~~women and that is in line with the fact that~~ drugs were also used more often in men. The higher use may be explained by the higher prevalence of ischemic heart disease (IHD). However, studies have shown that these drugs are under-used for secondary prevention ~~studies show an underuse of lipid lowering drugs~~ in women.[~~10 35-37~~29-32] Reasons for this ~~underuse~~ could be that women suffer more from myalgia as an adverse reaction[~~38~~33] but also that women are older and have more co-morbidity when suffering from cardiovascular disease~~. The latter could lead to that doctors hesitate to prescribe~~, thus receiving less intensive secondary preventive medication ~~to women in spite of actual guidelines.~~

~~Older age in women could also explain gender difference in the use of~~ Men used more anticoagulants. ~~One of the~~ The most common ~~indications~~indication for anticoagulants is atrial fibrillation, a condition more commonly found in men but carrying a higher risk of fatal complications like embolic stroke, for women.[~~39~~34] Underuse of anticoagulants in women with atrial fibrillation has been shown in earlier studies.[~~10~~29 ~~35~~32 ~~40-43~~35-38] Men are also prescribed anti-arrhythmic drugs to a higher degree than women. This may be ~~medically rational~~ appropriate as women have a higher risk of the fatal arrhythmia "torsade de pointe-ventricular tachycardia" induced by some anti-arrhythmics like sotalol and quinidine.[~~44~~39]

~~As shown in this study there are medically rational as well as irrational differences in drug utilisation between men and women. Whether these data from the whole of Sweden could be generalised to other countries is unknown. It is however plausible that the same international guidelines are used ant that in some diseases/conditions the background is the same in other countries. As data on sex differences in drug utilisation from other countries are sparse, we are planning cross-national studies.~~

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~~Healthcare professionals should aim to minimize inappropriate drug use in both genders. However, finding information about specific sex- and gender differences in pharmacokinetics and pharmacodynamics of different drugs can sometimes be both intricate and time consuming. Studies such like ours may help to raise awareness of irrational sex- and gender differences in drug utilisation and aid prescribers in their quest to provide a rational drug prescription. It is important to recognize that just providing data have a limited impact on prescribing patterns.[45] A potential way forward may be to include recommendations in interactive decision support systems integrated in the medical record.[46]~~

~~Strengths and limitations~~

The main strength of this study is the complete coverage ~~with~~of all dispensed prescription drugs to the entire Swedish population. This ~~provides~~provides a population-based overview of drug utilisation difficult to acquire in many other health systems. Furthermore, data on dispensed drugs is closer to the actual consumption than data on prescribed drugs, and it is free from recall- bias common in patient reported data.[40]

The most important limitation is the ~~registry-based design including the uncertainty about sensitivity and specificity using dispensing data to assess actual patient consumption patterns. Furthermore, the Swedish Prescribed Drug Register lacks clinical information on diagnosis and off-label prescribing enabling more in-depth analyses on the rational behind the observed differences. Also, international generalisibility of the findings is unknown mainly because population based studies from other countries' entire drug utilization are missing. We plan to perform such studies.~~lack of information on patient characteristics and clinical data to assess the rationale behind the observed differences. Furthermore, it is important to emphasize that gender differences may only be hypothesised from these data.

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~~**Conclusion**~~

~~When analysing prevalence and incidence of dispensed drugs~~In conclusion, in ~~the Swedish population medically unfounded~~ this large study we found substantial differences in drug utilisation between men and women ~~are found. This is~~. In an attempt to ~~our knowledge the first study of all dispensed drugs in an entire population of a country where not only the~~ explain these sex differences ~~are reported but attempts to explain~~ we searched the literature. Some sex disparities could be explained by differences ~~are made. While many differences seem well founded other rise questions of irrational use in one of the sexes.~~ in prevalence of disease or frequency of adverse reactions. Less medically justified explanations were also identified such as overestimation of risk vs. benefit in women compared to men. We also found suggestions that gender aspects such as societal acceptance of overweight in women compared to men may be involved. More research and a greater awareness of the influence of sex- and gender in health and disease are needed to ensure a rational ~~and medically rational prescription to all~~drug use in both men and women.

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Drug and Therapeutics Committee in Stockholm County Council for clinical comments on the study findings.

Contributors: KSG proposed the study. All authors developed the study design. DL conducted the analyses. All authors contributed to interpreting the data and drafting the manuscript.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare ~~and declare~~: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the regional Ethics Committee at Karolinska Institutet, Sweden. ~~Dnr~~Ref. no. 2010/788-31/5.

Data sharing: Proposals for data sharing should be sent to the corresponding author.

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Figure 1. Proportions of the Swedish population purchasing at least one prescribed drug in 2010 by age and sex.

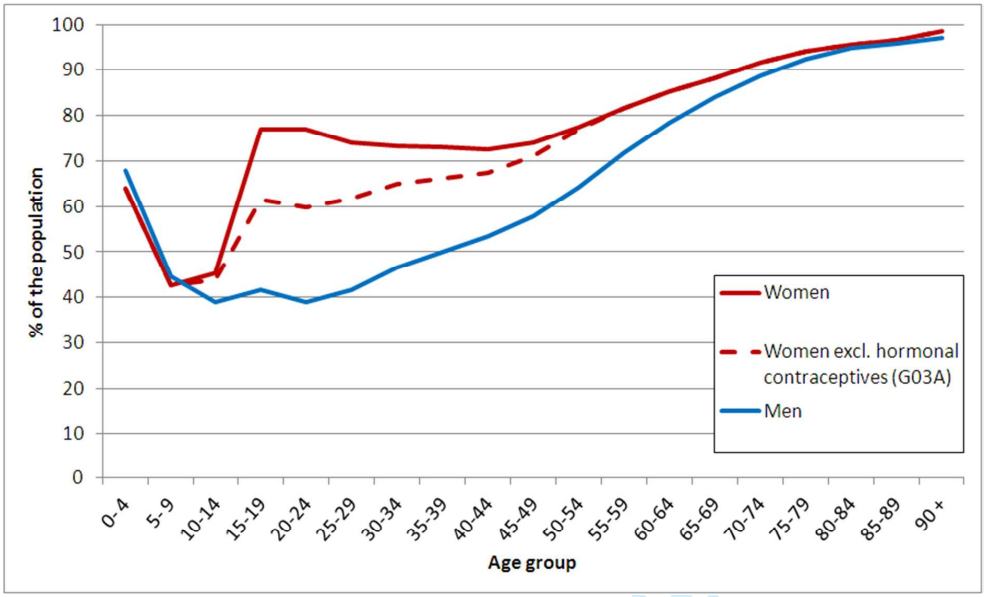
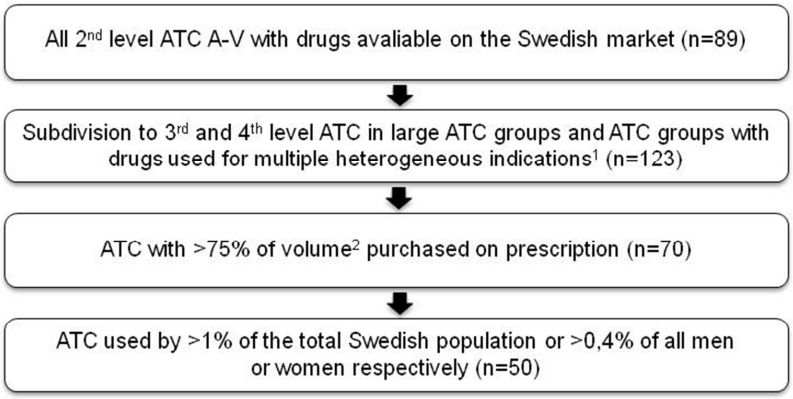


Figure 2. Flow chart showing the selection of pharmacological groups included in the specific analyses on sex- and gender differences in different therapeutic areas.



[1] Cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06) and ophthalmologicals (S01)

[2] Volume was measured in Defined Daily Doses (DDDs), except for eight ATC groups without any assigned DDD values where packages were used instead.

Figure 3. Pharmacological groups with the highest age adjusted relative differences in prevalence 2010.

ATC	Pharmacological group	PAT/TIN	
		Men	Women
J02	Antimycotics for systemic use	2.8	18.9
M05	Drugs for treatment of bone diseases	3.2	19.3
H03	Thyroid therapy	13.1	65.7
N02C	Antimigraine preparations	5.0	17.2
A12	Mineral supplements	16.2	57.3
A08	Antiobesity preparations	1.6	4.1
J05	Antivirals for systemic use	7.9	14.8
P01	Antiprotozoals	11.0	20.6
N06A	Antidepressants	55.4	106.6
H01	Pituitary and hypothalamic hormones	2.5	4.1
C09C+D	Angiotensin II antagonists and comb.	45.2	46.6
C08	Calcium channel blockers	60.8	59.6
C01A	Cardiac glycosides	6.0	6.8
C10	Lipid modifying agents	98.0	81.1
C01D	Vasodilators used in cardiac diseases	24.9	23.6
B01	Antithrombotic agents	109.8	97.7
A10	Drugs used in diabetes	45.3	34.5
C09A+B	ACE inhibitors and combinations	78.1	60.9
N06B	Psychostimulants	6.9	4.1
M04	Antigout preparations	12.2	5.9

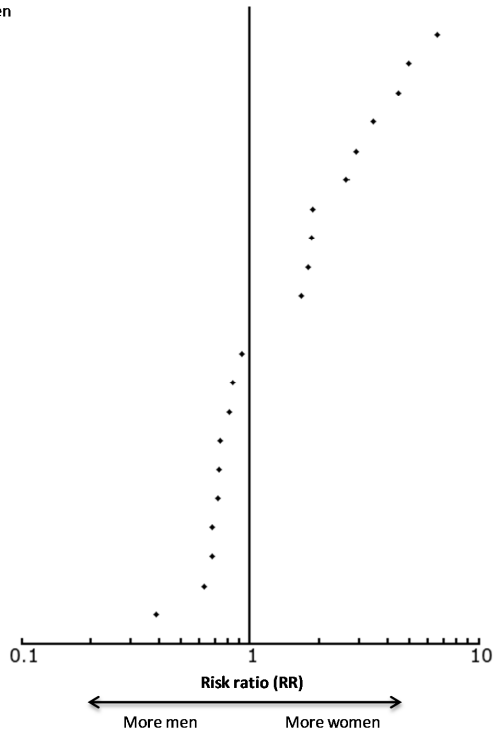


Table I. Sex differences in prevalence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups*. * The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/TIN = number of patients (men or women) per 1000 individuals. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/TIN		RR (95 C.I.)	
		Men	Women	Women/Men	
J02	Antimycotics for systemic use	2.75	18.90	6.87 (6.74-7.00)	6.56 (6.44-6.68)
M05	Drugs for treatment of bone diseases	3.19	19.28	6.04 (5.94-6.1	
H03	Thyroid therapy	13.12	65.67	5.00 (4.96-5.05)	4.46 (4.42-4.50)
N02C	Antimigraine Preparations	5.03	17.24	3.43 (3.38-3.48)	3.44 (3.39-3.49)
A12	Mineral supplements	16.19	57.29	3.54 (3.51-3.57)	2.90 (2.88-2.92)
A08	Antiobesity preparations	1.59	4.13	2.60 (2.53-2.67)	2.62 (2.55-2.69)
J05	Antivirals for systemic use	7.85	14.79	1.88 (1.86-1.91)	1.86 (1.84-1.89)
P01	Antiprotozoals	11.00	20.55	1.87 (1.85-1.89)	1.85 (1.83-1.87)
N06A	Antidepressants	55.35	106.60	1.93 (1.92-1.93)	1.79 (1.78-1.80)
H01	Pituitary and hypothalamic hormones and analogues	2.46	4.08	1.66 (1.62-1.7	
N05B	Anxiolytics	39.39	70.01	1.78 (1.77-1.79)	1.60 (1.59-1.61)
N05C	Hypnotics and sedatives	58.35	103.83	1.78 (1.77-1.79)	1.56 (1.56-1.57)
M03	Muscle relaxants	6.38	9.98	1.56 (1.54-1.59)	1.53 (1.51-1.56)
B03	Antianemic preparations	40.35	73.24	1.82 (1.81-1.83)	1.48 (1.47-1.49)
J01	Antibacterials for systemic use	191.26	265.58	1.39 (1.39-1.39)	1.36 (1.36-1.36)
L04	Immunosuppressants	7.32	10.05	1.37 (1.35-1.39)	1.33 (1.31-1.35)
G04BD	Urinary antispasmodics	6.12	9.61	1.57 (1.55-1.60)	1.33 (1.31-1.35)
A02	Drugs for acid related disorders	70.08	101.87	1.45 (1.45-1.4	
H02	Corticosteroids for systemic use	37.17	51.98	1.40 (1.39-1.41)	1.30 (1.30-1.31)
S01B	Anti-inflammatory agents	12.72	18.95	1.49 (1.47-1.50)	1.30 (1.29-1.31)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	13.77	19.35	1.40 (1.39-1.4	
N02A	Opioids	66.90	92.97	1.39 (1.38-1.40)	1.27 (1.27-1.28)
C03	Diuretics	59.48	92.83	1.56 (1.55-1.57)	1.24 (1.24-1.25)
S02	Otologicals	4.54	5.71	1.26 (1.24-1.28)	1.23 (1.21-1.25)
R03	Drugs for obstructive airway diseases	71.79	88.80	1.24 (1.23-1.2	
S03	Ophthalmological and otological preparations	23.31	28.38	1.22 (1.21-1.23)	1.18 (1.17-1.19)
N03	Antiepileptics	18.22	22.08	1.21 (1.20-1.22)	1.15 (1.14-1.16)

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N05A	Antipsychotics	13.59	16.51	1.21 (1.20-1.23)	1.11 (1.09-1.12)
N06D	Anti-dementia drugs	3.38	5.41	1.60 (1.57-1.63)	1.10 (1.07-1.12)
N04	Anti-parkinson drugs	6.83	8.49	1.24 (1.22-1.26)	1.06 (1.05-1.08)
S01E	Antiglaucoma preparations and miotics	13.57	18.49	1.36 (1.35-1.38)	1.02 (1.01-1.03)
L02	Endocrine therapy	6.34	7.60	1.20 (1.18-1.22)	0.96 (0.95-0.97)
C07	Beta blocking agents	97.82	107.57	1.10 (1.10-1.10)	0.94 (0.93-0.94)
C09C+D	Angiotensin II antagonists and combinations	45.16	46.56	1.03 (1.02-1.0	Formatted: English (U.S.)
C08	Calcium channel blockers	60.84	59.61	0.98 (0.97-0.98)	0.84 (0.84-0.84)
C01A	Cardiac glycosides	6.01	6.83	1.14 (1.12-1.16)	0.81 (0.79-0.82)
C10	Lipid modifying agents	98.03	81.05	0.83 (0.82-0.83)	0.74 (0.73-0.74)
C01D	Vasodilators used in cardiac diseases	24.94	23.61	0.95 (0.94-0.9	Formatted: English (U.S.)
B01	Antithrombotic agents	109.81	97.68	0.89 (0.89-0.89)	0.72 (0.72-0.73)
A10	Drugs used in diabetes	45.27	34.48	0.76 (0.76-0.77)	0.68 (0.68-0.69)
C09A+B	ACE-inhibitors and combinations	78.14	60.90	0.78 (0.78-0.78)	0.68 (0.67-0.68)
N06B	Psychostimulants	6.94	4.11	0.59 (0.58-0.60)	0.62 (0.61-0.64)
M04	Antigout preparations	12.24	5.91	0.48 (0.48-0.49)	0.38 (0.38-0.39)

*The following pharmacological groups are not presented in the table due to sex-specific indications; G02 Other gynecologicals (used by 9.~~8~~79 PAT/1000 women and 0.~~2~~20 PAT/1000 men), G03A Hormonal contraceptives (used by 132.~~1~~05 PAT/1000 women and 0.~~1~~08 PAT/1000 men), G03C Estrogens (used by 69.~~6~~62 PAT/1000 women and 0.~~1~~08 PAT/1000 men), G03D Progestogens (used by 15.~~9~~90 PAT/1000 women and 0.~~0~~03 PAT/1000 men), G03F Progestogens and estrogens in combination (used by 12.~~3~~26 PAT/1000 women and 0.~~0~~00 PAT/1000 men), G04C Drugs used in benign prostatic hypertrophy (used by 0.~~3~~25 PAT/1000 women and 26.~~2~~23 PAT/1000 men) and G04BE Drugs used in erectile dysfunction (used by 25.~~4~~38 PAT/1000 men and 0.~~1~~07 PAT/1000 women).

Table II. Sex differences in incidence of drug therapy in Sweden 2010 by pharmacological group. Crude and age adjusted relative differences for included ATC groups*. * The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/1000 PYs = number of patients (men or women) per 1000 patient-years. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/1000 PYs		RR (95 C.I.)	
		Men	Women	Women/Men	
J02	Antimycotics for systemic use	2.28	13.23	5.80 (5.68-5.92)	5.49 (5.38-5.60)
H03	Thyroid therapy	1.55	5.77	3.72 (3.62-3.81)	3.49 (3.40-3.58)
M05	Drugs for treatment of bone diseases	0.97	3.98	4.11 (3.98-4.2	
N02C	Antimigraine Preparations	1.89	4.99	2.64 (2.57-2.70)	2.67 (2.61-2.74)
A08	Antiobesity preparations	0.55	1.41	2.57 (2.45-2.69)	2.60 (2.48-2.72)
H01	Pituitary and hypothalamic hormones and analogues	0.99	2.45	2.47 (2.38-2.5	
A12	Mineral supplements	5.82	14.85	2.55 (2.52-2.59)	2.21 (2.18-2.24)
J05	Antivirals for systemic use	4.60	8.53	1.85 (1.82-1.89)	1.80 (1.77-1.83)
P01	Antiprotozoals	9.38	16.83	1.80 (1.77-1.82)	1.79 (1.76-1.81)
B03	Antianemic preparations	12.28	23.72	1.93 (1.91-1.95)	1.70 (1.68-1.72)
N06A	Antidepressants	15.35	24.71	1.61 (1.59-1.62)	1.52 (1.51-1.54)
L02	Endocrine therapy	1.37	2.43	1.78 (1.73-1.84)	1.52 (1.48-1.56)
N05B	Anxiolytics	17.90	28.41	1.59 (1.57-1.60)	1.47 (1.46-1.48)
M03	Muscle relaxants	4.50	6.67	1.48 (1.46-1.51)	1.46 (1.44-1.49)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	6.68	10.27	1.39 (1.37-1.4	
A02	Drugs for acid related disorders	25.47	37.35	1.47 (1.46-1.4	
N05C	Hypnotics and sedatives	18.90	26.94	1.43 (1.41-1.44)	1.32 (1.31-1.34)
S01B	Anti-inflammatory agents	9.27	13.71	1.48 (1.46-1.50)	1.29 (1.27-1.31)
H02	Corticosteroids for systemic use	21.36	28.28	1.32 (1.31-1.33)	1.27 (1.26-1.28)
N03	Antiepileptics	4.76	6.29	1.32 (1.30-1.35)	1.25 (1.22-1.27)
L04	Immunosuppressants	1.43	1.80	1.26 (1.22-1.30)	1.23 (1.20-1.27)
J01	Antibacterials for systemic use	126.14	153.73	1.22 (1.21-1.22)	1.21 (1.20-1.21)
R03	Drugs for obstructive airway diseases	27.19	32.11	1.18 (1.17-1.1	
N04	Anti-parkinson drugs	1.67	2.26	1.35 (1.31-1.39)	1.19 (1.15-1.22)
S02	Otologicals	3.39	4.04	1.19 (1.17-1.22)	1.17 (1.14-1.19)
N02A	Opioids	39.55	48.30	1.22 (1.21-1.23)	1.14 (1.14-1.15)
C03	Diuretics	10.63	14.35	1.35 (1.33-1.37)	1.14 (1.13-1.15)
S03	Ophthalmological and otological preparations	18.43	21.41	1.16 (1.15-1.17)	1.14 (1.13-1.15)

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G04BD	Urinary antispasmodics	2.63	3.33	1.27 (1.24-1.30)	1.10 (1.08-1.13)
N05A	Antipsychotics	3.27	4.03	1.23 (1.21-1.26)	1.07 (1.05-1.10)
N06D	Anti-dementia drugs	0.91	1.38	1.52 (1.46-1.58)	1.07 (1.03-1.11)
B01	Antithrombotic agents	15.05	17.48	1.16. (1.15-1.7)	1.05 (1.04-1.06)
C07	Beta blocking agents	12.16	13.61	1.12 (1.11-1.13)	1.02 (1.01-1.03)
S01E	Antiglaucoma preparations and miotics	1.90	2.15	1.13 (1.10-1.16)	0.96 (0.93-0.98)
C09C+D	Angiotensin II antagonists and combinations	6.18	6.42	1.04 (1.02-1.0	Formatted: English (U.S.)
C08	Calcium channel blockers	10.35	10.72	1.04 (1.02-1.05)	0.93 (0.92-0.94)
C01A	Cardiac glycosides	1.09	1.24	1.14 (1.10-1.18)	0.86 (0.82-0.89)
C09A+B	ACE-inhibitors and combinations	14.28	13.11	0.92 (0.91-0.93)	0.83 (0.82-0.84)
C10	Lipid modifying agents	13.01	11.28	0.87 (0.86-0.88)	0.81 (0.80-0.82)
A10	Drugs used in diabetes	4.83	3.79	0.79 (0.77-0.80)	0.73 (0.72-0.75)
N06B	Psychostimulants	2.36	1.57	0.67 (0.65-0.69)	0.70 (0.68-0.72)
C01D	Vasodilators used in cardiac diseases	8.34	6.93	0.83 (0.82-0.8	Formatted: English (U.S.)
M04	Antigout preparations	2.71	1.44	0.53 (0.51-0.55)	0.44 (0.42-0.45)

*The following pharmacological groups were excluded from the table due to sex-specific indications; G02 Other gynecologicals (used by 5.33 PAT/1000 PYs among women and 0.03 PAT/1000 PYs among men), G03A Hormonal contraceptives (used by 42.09 PAT/1000 PYs among women and 0.04 PAT/1000 PYs among men), G03C Estrogens (used by 16.44 PAT/1000 PYs among women and 0.03 PAT/1000 PYs among men), G03D Progestogens (used by 11.20 PAT/1000 PYs among women and 0.01 PAT/1000 PYs among men), G03F Progestogens and estrogens in combination (used by 2.56 PAT/1000 PYs among women and 0.00 PAT/1000 PYs among men), G04C Drugs used in benign prostatic hypertrophy (used by 0.20 PAT/1000 PYs among women and 7.34 PAT/1000 PYs among men) and G04BE Drugs used in erectile dysfunction (used by 0.03 PAT/1000 PYs among women and 10.16 PAT/1000 PYs among men).

Article Summary

Article ~~focus'~~focus

- To analyse ~~the pharmaceutical~~ drug ~~use~~utilisation in a whole country
- To ~~make a sex- and gender analysis~~identify areas of potential discrepancies in drug use patterns between men and women

~~To analyse reasons behind irrational drug use~~

- 'To review existing literature for explanations for differences in drug use between men and women
- To raise awareness for drug use differences between men and women which may not be rational

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Key messages'

- Differences in drug utilisation between men and women in both prevalence and incidence were found in Sweden overall, and for 48 of 50 pharmacological groups.
- Many sex differences in drug use in our study may be explained by sex differences in morbidity or biology. Other differences are hard to explain on medical grounds and may indicate unequal treatment.
- There are few studies analysing the rational of the observed sex differences.

~~**Strengths and limitations of this study**~~

~~Registry based design include uncertainty about sensitivity and specificity using dispensing data to assess actual patient consumption patterns. The Swedish Prescribed Drug Register lacks clinical information on diagnosis and off label prescribing and thus unenabling more in-depth analyses.~~

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	na

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	na
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	na
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	na
		Cross-sectional study—Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table 1. Proportions of the Swedish population purchasing at least one prescribed drug in 2010 by age and sex.

Age group	Men (%)	Women (%)	Women excl. hormonal contraceptives (G03A) (%)
0- 4	68	64	64
5- 9	45	43	43
10-14	39	45	44
15-19	42	77	62
20-24	39	77	60
25-29	42	74	62
30-34	46	73	65
35-39	50	73	66
40-44	53	73	67
45-49	58	74	71
50-54	64	78	77
55-59	72	82	82
60-64	79	85	85
65-69	84	88	88
70-74	89	92	92
75-79	93	94	94
80-84	95	96	96
85-89	96	96	96
90 +	97	99	99
Total	*59*	*76*	*71*

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Differences in drug utilisation between men and women - a cross sectional analysis of all dispensed drugs in Sweden

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Keywords:	EPIDEMIOLOGY, GENERAL MEDICINE (see Internal Medicine), PUBLIC HEALTH

Title:

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Abstract

Objectives: Differences between men and women are important to take into account when prescribing drugs. There is a lack of comprehensive overviews on sex differences in drug utilisation. Therefore, we analysed the prevalence and incidence of drug utilisation in all Swedish men and women.

Design: Cross-sectional population database analysis

Methods: Data on all dispensed drugs in 2010 to the entire Swedish population (9.3 million inhabitants) were obtained from the Swedish Prescribed Drug Register. All pharmacological groups with ambulatory care prescribing accounting for >75% of the total volume in Defined Daily Doses (DDDs) and a prevalence of >1% were included in the analysis. Crude and age adjusted difference in prevalence and incidence were calculated as risk ratios (RR) of women/men.

Results: In all, 2.8 million men (59%) and 3.6 million women (76%) purchased at least one prescribed drug during 2010. Women purchased more prescription drugs in all age groups except among children under the age of 10. The largest sex difference in prevalence in absolute numbers was found for antibiotics that were more common in women, 265.5 patients (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (65.7 PAT/1000 women and 13.1 PAT/1000 men), and antidepressants (106.6 PAT/1000 women and 55.4 PAT/1000 men). Age adjusted relative sex differences in prevalence were found in 48 of the 50 identified pharmacological groups. The pharmacological groups with the largest relative differences of dispensed drugs with higher utilisation in women were antimycotics for systemic use (RR 6.6 CI 6.4-6.7), drugs for osteoporosis (RR 4.9 CI 4.9-5.0) and thyroid therapy (RR 4.5 CI 4.4-4.5), while in men the

utilisation was higher for antigout agents(RR 0.4 CI 0.4-0.4), psychostimulants (RR 0.6 CI 0.6-0.6) and ACE inhibitors (angiotensin-converting-enzyme inhibitors) (RR 0.7 CI 0.7-0.7).

Conclusion: Substantial differences in drug utilisation between men and women were found. Some differences may be rational and desirable related to differences between the sexes in incidence or prevalence of disease or by biologic differences. Other differences are more difficult to explain on medical grounds and may indicate unequal treatment.

Introduction

Drug therapy plays an important role in preserving people's health and improving their quality of life. Consequently, drugs are the most important treatment options for most diseases and the majority of medical consultations result in a prescription.[1] Furthermore, pharmaceuticals also constitute a significant proportion of healthcare spending, more rapidly increasing than other healthcare components in many countries.[2 3] In Sweden, pharmaceuticals accounted for 12.6 % of the total health care expenditure in 2010,[4] but the growth has been moderated after the implementation of major reforms.[5]

Rational drug use implies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community".[6] Individual requirements indicate that not only severity of disease, co-morbidity, renal function and age should be considered, but also sex and gender. While it is evident that biological differences, commonly referred to as "sex differences", should be considered when prescribing medicines, it is unclear to what extent socio-cultural differences, commonly referred to as "gender differences" should be considered by the prescribing physician. Sex differences in drug utilisation have been demonstrated in several therapeutic areas.[7-11] However, there is a lack of both comprehensive overviews on sex- and gender differences of drug utilisation in entire populations and especially studies analysing the rationale of the observed differences. Variations in morbidity may explain some differences, whereas other differences may indicate inequities and under- or overuse of certain drugs in men or women.

The aim of this study was to analyse differences in prevalence and incidence of drug utilisation among men and women in the Swedish population and problematise the observed differences.

Methods

This was a cross-sectional study analysing sex differences in prevalence and incidence of drug use in ambulatory care in Sweden 2010, overall and within different pharmacological groups. Data were collected from the Swedish Prescribed Drug Register (SPDR), which contains complete data (>99 % coverage) with unique identifiers of all prescribed drugs (irrespective of reimbursement) dispensed to the entire Swedish population of 9.3 million inhabitants.[12,13]

The period prevalence was defined as the proportion of the population in the country purchasing ≥1 prescription in 2010 and measured in number of patients exposed per 1000 inhabitants (PAT/TIN). Incidence was defined as the proportion of the population redeeming their first prescription in 2010 after a one-year wash-out period with no dispensation and was measured in number of patients per 1000 person-years (PAT/1000 PYs).

Pharmacological groups were selected by using the following procedure:

1. All 89 Anatomical Therapeutic Chemical (ATC) 2nd level groups with drugs available on the Swedish market[14,15] were identified.
2. In large ATC groups and ATC groups with drugs used for multiple heterogeneous indications, i.e. cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06), ophthalmologicals (S01), a subdivision was done to ATC 3rd or 4th level to attain a more clinically relevant description of the utilisation.
3. ATC groups with less than 75% of the total sales volume in the country purchased on prescription were excluded since sex distribution was not possible to collect for those purchased over-the-counter (OTC) or used in inpatient care. Volume was measured in

Defined Daily Doses (DDDs), except for eight pharmacological groups for which there were no DDDs assigned.[15] For these groups, packages were used as volume measure. Calculations of the proportion of the total volume purchased as prescriptions in ambulatory care were based on aggregated sales data from all Swedish pharmacies.

4. For the identified ATC groups at various hierarchical levels, groups that were purchased by less than 1% of the total Swedish population or purchased by less than 0.4% of men or women, respectively, were excluded to avoid random variation due to small numbers.

Crude and age adjusted values were calculated. Age standardisation was performed by direct standardisation, where the Swedish population on 31 December 2009 (4 649 014 men and 4 691 668 women[13]) was used as the standard population. In the calculations, 5-year age groups were used. Differences between the sexes were calculated as a risk ratio (RR) of women/men with 95% confidence intervals (CI). All analyses were performed in Microsoft Excel 2007 and SAS ver. 9.2 (SAS Institute, Cary, NC) using descriptive statistical methods.

Results

In 2010, the total volume of drugs sold in Sweden was 5.8 billion Defined Daily Doses (DDD), corresponding to 1715 DDD/1000 inhabitants daily. The total expenditures were 35.6 billion Swedish Kronor (SEK) (100 SEK = 8.96 GBP, September 2012). Drugs prescribed in ambulatory care, and thus included in the study, accounted for 88 % of the total volume and 72 % of the total expenditures on drugs in the country.

In all, 2.8 million men (59%) and 3.6 million women (76%), purchased at least one prescribed drug during 2010. The older the patient, the higher the likelihood of drug purchase. Women purchased more prescription drugs in all age groups except among children under the age of 10, even when hormonal contraceptives were excluded (Table 1).

Crude sex differences in prevalence were found in 48 of the 50 pharmacological ATC groups included (Figure 1, Table 2). After age adjustment, sex differences remained in 48 ATC groups. For antiglaucoma (S01E) and endocrine drugs (L02), the sex differences disappeared after age adjustment, while the opposite was seen for ARBs (angiotensin II receptor blockers) (C09C+D) and calcium channel blockers (C08), with a slightly higher utilisation in men after age adjustment. Beta blocking agents (C07) and cardiac glycosides (C01A) were more common in women before age adjustment, but were found to be more common in men after adjustment. The large differences in drugs for treatment of bone diseases (M05), thyroid therapy (H03), mineral supplements (A12) and anti-dementia drugs (N06D) diminished after age adjustment, even though the higher utilisation in women remained (Table 2).

The pharmacological groups with the largest relative differences with higher utilisation in women were antimycotics for systemic use (RR 6.6), drugs for osteoporosis (RR 4.9) and

thyroid therapy (RR 4.5), while the utilisation was higher in men for antigout preparations (RR 0.4), psychostimulants (0.6) and ACE-inhibitors (RR 0.7) (Figure 2).

The largest sex difference in absolute numbers was found for systemic antibacterials (J01) that were more common in women, 265.5 patients exposed (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (H03), purchased by 65.7 PAT/1000 women and 13.1 PAT/1000 men, and antidepressants (N06A), purchased by 106.6 PAT/1000 women and 55.4 PAT/1000 men.

The incidence showed a similar pattern as the prevalence (Table 3). However, the sex differences were substantially higher for endocrine therapy (L02) and urinary antispasmodic agents (G04BD). Before age adjustment, 40 pharmacological groups were more frequently dispensed to women and eight groups to men. After age adjustment, sex differences remained in 36 and 11 ATC-groups for women and men, respectively. In only one pharmacological group, drugs for treatment of bone diseases (M05), the sex difference diminished substantially after age adjustment.

Discussion

This drug utilisation study shows substantial sex differences in purchases of prescription drugs in Sweden. It is obvious that some of these differences may be explained by variations in disease prevalence, severity of disease, pathophysiology, diagnostics and treatment response or by other biologic differences such as those induced by pregnancy and/or lactation. However, it is also evident that other differences lack a rational medical explanation.

Throughout their lifespan, women have more contact with the health care system, which provides them with an extra opportunity for detection of disease. In the pre-menopausal years, a woman's need for contraceptives, pregnancy and childbirth and, in the peri- and postmenopausal period, screening programs for breast and cervical cancers and gynecological disorders require health care consultations.[16]Also, chronic disabling diseases associated with a chronic need for medication, such as musculoskeletal disorders, are more common in women than men.[17] From a gender perspective, studies have shown that men are less prone to seek preventive health care.[18]

Some differences between the sexes were expected. The higher utilisation of antimycotics in women could partly be explained by gynecological infections such as vaginitis. Also, the 4.5 times higher utilisation of thyroid therapy corresponds to a four times higher prevalence of impaired thyroid function in women.[19] The sex difference in utilisation of anti migraine drugs could be explained by a two to three times higher prevalence of migraine among women.[20] Men purchased more psychostimulants, corresponding well to a higher prevalence of ADHD[21] and autism[22].

A large sex difference was observed for antibiotics. Men are more susceptible to infections than women in general, yet we found a higher absolute utilisation of antibiotics in women. A common reason for prescribing antibiotics in primary care is urinary tract infection (UTI), which is much more prevalent in women.[23] An overdiagnosis of this condition in women has, however, been reported, which could potentially explain some of the higher utilisation in women.[24]Women were dispensed more anti-obesity drugs than men in spite of obesity being more common in men.[25 26] Also, more women than men undergo obesity surgery.[27] There are reasons to believe that the sociocultural pressure for women to be slim is higher than for men which could explain this prescription pattern.

In the cardiovascular field several differences in utilisation of prescribed drugs were found. ACE inhibitors, primarily used for the treatment of heart failure and hypertension with the same prevalence in both sexes, were purchased by men to a larger extent. This may be due to the higher frequency of coughing as an adverse event in women.[28] However, the alternative treatment ARB was purchased by women and men to the same extent. Our findings may therefore indicate an under-use of renin-angiotensin-agents in women. Lipid lowering drugs were also purchased more frequently by men. The higher utilisation may be explained by the higher prevalence of ischemic heart disease (IHD). However, studies have shown that these drugs are under-used for secondary prevention in women[29-32]. Reasons for this could be that women suffer more from myalgia as an adverse reaction[33] but also that women are older and have more co-morbidity when suffering from cardiovascular disease, thus receiving less intensive secondary preventive medication.

Men were dispensed more anticoagulants. The most common indication for anticoagulants is atrial fibrillation, a condition more commonly found in men but carrying a higher risk of fatal complications like embolic stroke, for women.[34] Under-utilisation of anticoagulants in women with atrial fibrillation has been shown in earlier studies.[29 32 35-38] Men were also dispensed anti-arrhythmic drugs to a higher degree than women. This may be appropriate as women have a higher risk of the fatal arrhythmia “torsade de pointe-ventricular tachycardia” induced by some anti-arrhythmics like sotalol and quinidine.[39]

The main strength of this study is the complete coverage of all dispensed prescription drugs to the entire Swedish population. This provides a population-based overview of drug utilisation difficult to acquire in many other health systems. Furthermore, data on dispensed drugs is closer to the actual consumption than data on prescribed drugs, and it is free from recall bias common in patient reported data.[40]

The most important limitation is the lack of information on patient characteristics and clinical data to assess the rationale behind the observed differences. Furthermore, it is important to emphasise that gender differences may only be hypothesised from these data.

In conclusion, in this large study we found substantial differences in drug utilisation between men and women. In an attempt to explain these sex differences we searched the literature. Some sex disparities could be explained by differences in prevalence of disease or frequency of adverse reactions. Less medically justified explanations were also identified such as overestimation of risk vs. benefit in women compared to men. We also found suggestions that gender aspects such as societal acceptance of overweight in women compared to men may be involved. More research and a greater awareness of the influence of sex- and gender in health and disease are needed to ensure rational drug use in both men and women.

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Contributors: KSG proposed the study. All authors developed the study design. DL conducted the analyses. All authors contributed to interpreting the data and drafting the manuscript.

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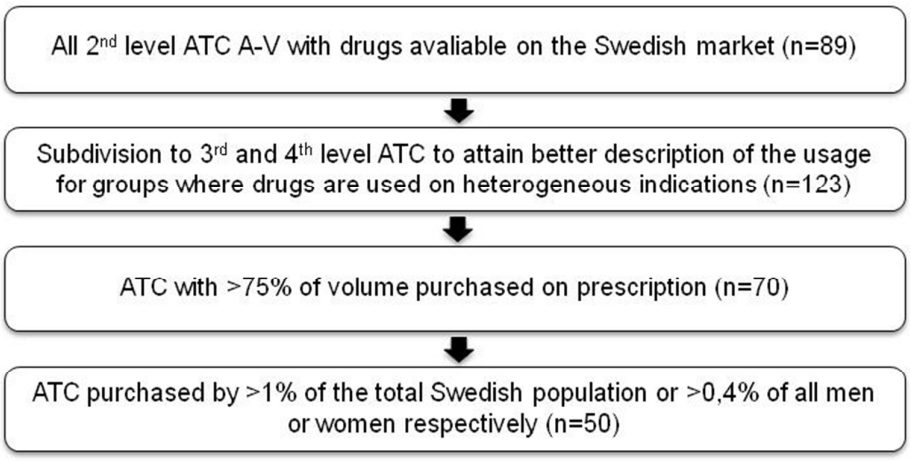
Ethical approval: The study was approved by the regional Ethics Committee at Karolinska Institutet, Sweden. Ref. no. 2010/788-31/5.

Data sharing: Proposals for data sharing should be sent to the corresponding author.

Figure 1. Flow chart showing the selection of pharmacological groups included in the specific analyses on sex- and gender differences in different therapeutic areas.



[1] Cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06) and ophthalmologicals (S01)

[2] Volume was measured in Defined Daily Doses (DDDs), except for eight ATC groups without any assigned DDD values where packages were used instead.

Figure 2. Pharmacological groups with the highest age adjusted relative differences in prevalence 2010.

ATC	Pharmacological group	PAT/TIN	
		Men	Women
J02	Antimycotics for systemic use	2.8	18.9
M05	Drugs for treatment of bone diseases	3.2	19.3
H03	Thyroid therapy	13.1	65.7
N02C	Antimigraine preparations	5.0	17.2
A12	Mineral supplements	16.2	57.3
A08	Antiobesity preparations	1.6	4.1
J05	Antivirals for systemic use	7.9	14.8
P01	Antiprotozoals	11.0	20.6
N06A	Antidepressants	55.4	106.6
H01	Pituitary and hypothalamic hormones	2.5	4.1
C09C+D	Angiotensin II antagonists and comb.	45.2	46.6
C08	Calcium channel blockers	60.8	59.6
C01A	Cardiac glycosides	6.0	6.8
C10	Lipid modifying agents	98.0	81.1
C01D	Vasodilators used in cardiac diseases	24.9	23.6
B01	Antithrombotic agents	109.8	97.7
A10	Drugs used in diabetes	45.3	34.5
C09A+B	ACE inhibitors and combinations	78.1	60.9
N06B	Psychostimulants	6.9	4.1
M04	Antigout preparations	12.2	5.9

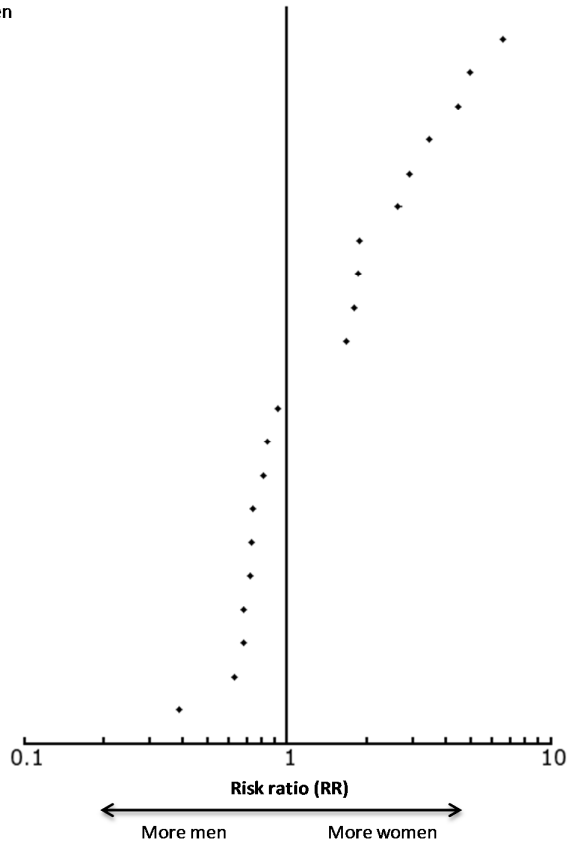


Table 1. Proportions of the Swedish population purchasing at least one prescribed drug in 2010, by age and sex.

Age group	Men (%)	Women (%)	Women excl. hormonal contraceptives (G03A) (%)
0- 4	68	64	64
5- 9	45	43	43
10-14	39	45	44
15-19	42	77	62
20-24	39	77	60
25-29	42	74	62
30-34	46	73	65
35-39	50	73	66
40-44	53	73	67
45-49	58	74	71
50-54	64	78	77
55-59	72	82	82
60-64	79	85	85
65-69	84	88	88
70-74	89	92	92
75-79	93	94	94
80-84	95	96	96
85-89	96	96	96
90 +	97	99	99
Total	*59*	*76*	*71*

Table II. Sex differences in prevalence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/TIN = number of patients (men or women) per 1000 individuals. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/TIN		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.75	18.90	6.87 (6.74-7.00)	6.56 (6.44-6.68)
M05	Drugs for treatment of bone diseases	3.19	19.28	6.04 (5.94-6.14)	4.95 (4.87-5.03)
H03	Thyroid therapy	13.12	65.67	5.00 (4.96-5.05)	4.46 (4.42-4.50)
N02C	Antimigraine Preparations	5.03	17.24	3.43 (3.38-3.48)	3.44 (3.39-3.49)
A12	Mineral supplements	16.19	57.29	3.54 (3.51-3.57)	2.90 (2.88-2.92)
A08	Antiobesity preparations	1.59	4.13	2.60 (2.53-2.67)	2.62 (2.55-2.69)
J05	Antivirals for systemic use	7.85	14.79	1.88 (1.86-1.91)	1.86 (1.84-1.89)
P01	Antiprotozoals	11.00	20.55	1.87 (1.85-1.89)	1.85 (1.83-1.87)
N06A	Antidepressants	55.35	106.60	1.93 (1.92-1.93)	1.79 (1.78-1.80)
H01	Pituitary and hypothalamic hormones and analogues	2.46	4.08	1.66 (1.62-1.70)	1.66 (1.63-1.70)
N05B	Anxiolytics	39.39	70.01	1.78 (1.77-1.79)	1.60 (1.59-1.61)
N05C	Hypnotics and sedatives	58.35	103.83	1.78 (1.77-1.79)	1.56 (1.56-1.57)
M03	Muscle relaxants	6.38	9.98	1.56 (1.54-1.59)	1.53 (1.51-1.56)
B03	Antianemic preparations	40.35	73.24	1.82 (1.81-1.83)	1.48 (1.47-1.49)
J01	Antibacterials for systemic use	191.26	265.58	1.39 (1.39-1.39)	1.36 (1.36-1.36)
L04	Immunosuppressants	7.32	10.05	1.37 (1.35-1.39)	1.33 (1.31-1.35)
G04BD	Urinary antispasmodics	6.12	9.61	1.57 (1.55-1.60)	1.33 (1.31-1.35)
A02	Drugs for acid related disorders	70.08	101.87	1.45 (1.45-1.46)	1.31 (1.31-1.32)
H02	Corticosteroids for systemic use	37.17	51.98	1.40 (1.39-1.41)	1.30 (1.30-1.31)
S01B	Anti-inflammatory agents	12.72	18.95	1.49 (1.47-1.50)	1.30 (1.29-1.31)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	13.77	19.35	1.40 (1.39-1.42)	1.29 (1.28-1.30)
N02A	Opioids	66.90	92.97	1.39 (1.38-1.40)	1.27 (1.27-1.28)
C03	Diuretics	59.48	92.83	1.56 (1.55-1.57)	1.24 (1.24-1.25)
S02	Otologicals	4.54	5.71	1.26 (1.24-1.28)	1.23 (1.21-1.25)
R03	Drugs for obstructive airway diseases	71.79	88.80	1.24 (1.23-1.24)	1.20 (1.20-1.21)
S03	Ophthalmological and otological preparations	23.31	28.38	1.22 (1.21-1.23)	1.18 (1.17-1.19)

N03	Antiepileptics	18.22	22.08	1.21 (1.20-1.22)	1.15 (1.14-1.16)
N05A	Antipsychotics	13.59	16.51	1.21 (1.20-1.23)	1.11 (1.09-1.12)
N06D	Anti-dementia drugs	3.38	5.41	1.60 (1.57-1.63)	1.10 (1.07-1.12)
N04	Anti-parkinson drugs	6.83	8.49	1.24 (1.22-1.26)	1.06 (1.05-1.08)
S01E	Antiglaucoma preparations and miotics	13.57	18.49	1.36 (1.35-1.38)	1.02 (1.01-1.03)
L02	Endocrine therapy	6.34	7.60	1.20 (1.18-1.22)	0.96 (0.95-0.97)
C07	Beta blocking agents	97.82	107.57	1.10 (1.10-1.10)	0.94 (0.93-0.94)
C09C+D	Angiotensin II antagonists and combinations	45.16	46.56	1.03 (1.02-1.04)	0.91 (0.91-0.92)
C08	Calcium channel blockers	60.84	59.61	0.98 (0.97-0.98)	0.84 (0.84-0.84)
C01A	Cardiac glycosides	6.01	6.83	1.14 (1.12-1.16)	0.81 (0.79-0.82)
C10	Lipid modifying agents	98.03	81.05	0.83 (0.82-0.83)	0.74 (0.73-0.74)
C01D	Vasodilators used in cardiac diseases	24.94	23.61	0.95 (0.94-0.95)	0.73 (0.72-0.73)
B01	Antithrombotic agents	109.81	97.68	0.89 (0.89-0.89)	0.72 (0.72-0.73)
A10	Drugs used in diabetes	45.27	34.48	0.76 (0.76-0.77)	0.68 (0.68-0.69)
C09A+B	ACE-inhibitors and combinations	78.14	60.90	0.78 (0.78-0.78)	0.68 (0.67-0.68)
N06B	Psychostimulants	6.94	4.11	0.59 (0.58-0.60)	0.62 (0.61-0.64)
M04	Antigout preparations	12.24	5.91	0.48 (0.48-0.49)	0.38 (0.38-0.39)

*The following pharmacological groups are not presented in the table due to sex-specific indications; G02 Other gynecologicals (dispensed to 9.79 PAT/1000 women and 0.20 PAT/1000 men), G03A Hormonal contraceptives (dispensed to 132.05 PAT/1000 women and 0.08 PAT/1000 men), G03C Estrogens (dispensed to 69.62 PAT/1000 women and 0.08 PAT/1000 men), G03D Progestogens (dispensed to 15.90 PAT/1000 women and 0.03 PAT/1000 men), G03F Progestogens and estrogens in combination (dispensed to 12.26 PAT/1000 women and 0.00 PAT/1000 men), G04C Drugs used in benign prostatic hypertrophy (dispensed to 0.25 PAT/1000 women and 26.23 PAT/1000 men) and G04BE Drugs used in erectile dysfunction (dispensed to 25.38 PAT/1000 men and 0.07 PAT/1000 women).

Table III. Sex differences in incidence of drug therapy in Sweden 2010 by pharmacological group. Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/1000 PYs = number of patients (men or women) per 1000 patient-years. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/1000 PYs		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.28	13.23	5.80 (5.68-5.92)	5.49 (5.38-5.60)
H03	Thyroid therapy	1.55	5.77	3.72 (3.62-3.81)	3.49 (3.40-3.58)
M05	Drugs for treatment of bone diseases	0.97	3.98	4.11 (3.98-4.24)	3.49 (3.38-3.60)
N02C	Antimigraine Preparations	1.89	4.99	2.64 (2.57-2.70)	2.67 (2.61-2.74)
A08	Antiobesity preparations	0.55	1.41	2.57 (2.45-2.69)	2.60 (2.48-2.72)
H01	Pituitary and hypothalamic hormones and analogues	0.99	2.45	2.47 (2.38-2.55)	2.48 (2.40-2.57)
A12	Mineral supplements	5.82	14.85	2.55 (2.52-2.59)	2.21 (2.18-2.24)
J05	Antivirals for systemic use	4.60	8.53	1.85 (1.82-1.89)	1.80 (1.77-1.83)
P01	Antiprotozoals	9.38	16.83	1.80 (1.77-1.82)	1.79 (1.76-1.81)
B03	Antianemic preparations	12.28	23.72	1.93 (1.91-1.95)	1.70 (1.68-1.72)
N06A	Antidepressants	15.35	24.71	1.61 (1.59-1.62)	1.52 (1.51-1.54)
L02	Endocrine therapy	1.37	2.43	1.78 (1.73-1.84)	1.52 (1.48-1.56)
N05B	Anxiolytics	17.90	28.41	1.59 (1.57-1.60)	1.47 (1.46-1.48)
M03	Muscle relaxants	4.50	6.67	1.48 (1.46-1.51)	1.46 (1.44-1.49)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	6.68	10.27	1.39 (1.37-1.41)	1.39 (1.37-1.41)
A02	Drugs for acid related disorders	25.47	37.35	1.47 (1.46-1.48)	1.38 (1.37-1.39)
N05C	Hypnotics and sedatives	18.90	26.94	1.43 (1.41-1.44)	1.32 (1.31-1.34)
S01B	Anti-inflammatory agents	9.27	13.71	1.48 (1.46-1.50)	1.29 (1.27-1.31)
H02	Corticosteroids for systemic use	21.36	28.28	1.32 (1.31-1.33)	1.27 (1.26-1.28)
N03	Antiepileptics	4.76	6.29	1.32 (1.30-1.35)	1.25 (1.22-1.27)
L04	Immunosuppressants	1.43	1.80	1.26 (1.22-1.30)	1.23 (1.20-1.27)
J01	Antibacterials for systemic use	126.14	153.73	1.22 (1.21-1.22)	1.21 (1.20-1.21)
R03	Drugs for obstructive airway diseases	27.19	32.11	1.18 (1.17-1.19)	1.19 (1.18-1.20)
N04	Anti-parkinson drugs	1.67	2.26	1.35 (1.31-1.39)	1.19 (1.15-1.22)
S02	Otologicals	3.39	4.04	1.19 (1.17-1.22)	1.17 (1.14-1.19)

N02A	Opioids	39.55	48.30	1.22 (1.21-1.23)	1.14 (1.14-1.15)
C03	Diuretics	10.63	14.35	1.35 (1.33-1.37)	1.14 (1.13-1.15)
S03	Ophthalmological and otological preparations	18.43	21.41	1.16 (1.15-1.17)	1.14 (1.13-1.15)
G04BD	Urinary antispasmodics	2.63	3.33	1.27 (1.24-1.30)	1.10 (1.08-1.13)
N05A	Antipsychotics	3.27	4.03	1.23 (1.21-1.26)	1.07 (1.05-1.10)
N06D	Anti-dementia drugs	0.91	1.38	1.52 (1.46-1.58)	1.07 (1.03-1.11)
B01	Antithrombotic agents	15.05	17.48	1.16. (1.15-1.7)	1.05 (1.04-1.06)
C07	Beta blocking agents	12.16	13.61	1.12 (1.11-1.13)	1.02 (1.01-1.03)
S01E	Antiglaucoma preparations and miotics	1.90	2.15	1.13 (1.10-1.16)	0.96 (0.93-0.98)
C09C+D	Angiotensin II antagonists and combinations	6.18	6.42	1.04 (1.02-1.05)	0.95 (0.93-0.96)
C08	Calcium channel blockers	10.35	10.72	1.04 (1.02-1.05)	0.93 (0.92-0.94)
C01A	Cardiac glycosides	1.09	1.24	1.14 (1.10-1.18)	0.86 (0.82-0.89)
C09A+B	ACE-inhibitors and combinations	14.28	13.11	0.92 (0.91-0.93)	0.83 (0.82-0.84)
C10	Lipid modifying agents	13.01	11.28	0.87 (0.86-0.88)	0.81 (0.80-0.82)
A10	Drugs used in diabetes	4.83	3.79	0.79 (0.77-0.80)	0.73 (0.72-0.75)
N06B	Psychostimulants	2.36	1.57	0.67 (0.65-0.69)	0.70 (0.68-0.72)
C01D	Vasodilators used in cardiac diseases	8.34	6.93	0.83 (0.82-0.84)	0.69 (0.68-0.70)
M04	Antigout preparations	2.71	1.44	0.53 (0.51-0.55)	0.44 (0.42-0.45)

*The following pharmacological groups were excluded from the table due to sex-specific indications; G02 Other gynecologicals (dispensed to 5.33 PAT/1000 PYs in women and 0.03 PAT/1000 PYs in men), G03A Hormonal contraceptives (dispensed to 42.09 PAT/1000 PYs in women and 0.04 PAT/1000 PYs in men), G03C Estrogens (dispensed to 16.44 PAT/1000 PYs in women and 0.03 PAT/1000 PYs in men), G03D Progestogens (dispensed to 11.20 PAT/1000 PYs in women and 0.01 PAT/1000 PYs in men), G03F Progestogens and estrogens in combination (dispensed to 2.56 PAT/1000 PYs in women and 0.00 PAT/1000 PYs in men), G04C Drugs used in benign prostatic hypertrophy (dispensed to 0.20 PAT/1000 PYs in women and 7.34 PAT/1000 PYs in men) and G04BE Drugs used in erectile dysfunction (dispensed to 0.03 PAT/1000 PYs in women and 10.16 PAT/1000 PYs in men).

Article Summary

Article focus

- To analyse drug utilisation in a whole country
- To identify areas of potential discrepancies in drug utilisation patterns between men and women
- To review existing literature for explanations for differences in drug utilisation between men and women
- To raise awareness about differences in drug utilisation between men and women which may not be rational

Key messages'

- Differences in drug utilisation between men and women in both prevalence and incidence were found in Sweden overall, and for 48 of 50 pharmacological groups.
- Many sex differences in drug utilisation in our study may be explained by sex differences in morbidity or biology. Other differences are hard to explain on medical grounds and may indicate unequal treatment.
- There are few studies analysing the rational of the observed sex differences.

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Title:

Differences in drug utilisation between men and women - a cross sectional analysis of all dispensed drugs in Sweden

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Abstract

Objectives: Differences between men and women are important to take into account when prescribing drugs. There is a lack of comprehensive overviews on sex differences in drug utilisation. Therefore, we analysed the prevalence and incidence of drug utilisation in all Swedish men and women.

Design: Cross-sectional population database analysis

Methods: Data on all dispensed drugs in 2010 to the entire Swedish population (9.3 million inhabitants) were obtained from the Swedish Prescribed Drug Register. All pharmacological groups with ambulatory care prescribing accounting for >75% of the total volume in Defined Daily Doses (DDDs) and a prevalence of >1% were included in the analysis. Crude and age adjusted difference in prevalence and incidence were calculated as risk ratios (RR) of women/men.

Results: In all, 2.8 million men (59%) and 3.6 million women (76%) purchased at least one prescribed drug during 2010. Women purchased more prescription drugs in all age groups except among children under the age of 10. The largest sex difference in prevalence in absolute numbers was found for antibiotics that were more common in women, 265.5 patients (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (65.7 PAT/1000 women and 13.1 PAT/1000 men), and antidepressants (106.6 PAT/1000 women and 55.4 PAT/1000 men). Age adjusted relative sex differences in prevalence were found in 48 of the 50 identified pharmacological groups. The pharmacological groups with the largest relative differences of dispensed drugs with higher utilisation in women were antimycotics for systemic use (RR 6.6 CI 6.4-6.7), drugs for osteoporosis (RR 4.9 CI 4.9-5.0) and thyroid therapy (RR 4.5 CI 4.4-4.5), while in men the

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utilisation was higher for antigout agents(RR 0.4 CI 0.4-0.4), psychostimulants (RR 0.6 CI 0.6-0.6) and ACE inhibitors (angiotensin-converting-enzyme inhibitors) (RR 0.7 CI 0.7-0.7).

Conclusion: Substantial differences in drug utilisation between men and women were found. Some differences may be rational and desirable related to differences between the sexes in incidence or prevalence of disease or by biologic differences. Other differences are more difficult to explain on medical grounds and may indicate unequal treatment.

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Introduction

Drug therapy plays an important role in preserving people's health and improving their quality of life. Consequently, drugs are the most important treatment options for most diseases and the majority of medical consultations result in a prescription.[1] Furthermore, pharmaceuticals also constitute a significant proportion of healthcare spending, more rapidly increasing than other healthcare components in many countries.[2 3] In Sweden, pharmaceuticals accounted for 12.6 % of the total health care expenditure in 2010,[4] but the growth has been moderated after the implementation of major reforms.[5]

Rational drug use implies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community".[6] Individual requirements indicate that not only severity of disease, co-morbidity, renal function and age should be considered, but also sex and gender. While it is evident that biological differences, commonly referred to as "sex differences", should be considered when prescribing medicines, it is unclear to what extent socio-cultural differences, commonly referred to as "gender differences" should be considered by the prescribing physician. Sex differences in drug utilisation have been demonstrated in several therapeutic areas.[7-11] However, there is a lack of both comprehensive overviews on sex- and gender differences of drug utilisation in entire populations and especially studies analysing the rationale of the observed differences. Variations in morbidity may explain some differences, whereas other differences may indicate inequities and under- or overuse of certain drugs in men or women.

The aim of this study was to analyse differences in prevalence and incidence of drug utilisation among men and women in the Swedish population and problematise the observed differences.

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Methods

This was a cross-sectional study analysing sex differences in prevalence and incidence of drug use in ambulatory care in Sweden 2010, overall and within different pharmacological groups. Data were collected from the Swedish Prescribed Drug Register (SPDR), which contains complete data (>99 % coverage) with unique identifiers of all prescribed drugs (irrespective of reimbursement) dispensed to the entire Swedish population of 9.3 million inhabitants.[12 13]

The period prevalence was defined as the proportion of the population in the country purchasing ≥1 prescription in 2010 and measured in number of patients exposed per 1000 inhabitants (PAT/TIN). Incidence was defined as the proportion of the population redeeming their first prescription in 2010 after a one-year wash-out period with no dispensation and was measured in number of patients per 1000 person-years (PAT/1000 PYs).

Pharmacological groups were selected by using the following procedure:

1. All 89 Anatomical Therapeutic Chemical (ATC) 2nd level groups with drugs available on the Swedish market[14 15] were identified.
2. In large ATC groups and ATC groups with drugs used for multiple heterogeneous indications, i.e. cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06), ophthalmologicals (S01), a subdivision was done to ATC 3rd or 4th level to attain a more clinically relevant description of the utilisation.
3. ATC groups with less than 75% of the total sales volume in the country purchased on prescription were excluded since sex distribution was not possible to collect for those purchased over-the-counter (OTC) or used in inpatient care. Volume was measured in

Defined Daily Doses (DDDs), except for eight pharmacological groups for which there were no DDDs assigned.[15] For these groups, packages were used as volume measure. Calculations of the proportion of the total volume purchased as prescriptions in ambulatory care were based on aggregated sales data from all Swedish pharmacies.

4. For the identified ATC groups at various hierarchical levels, groups that were purchased by less than 1% of the total Swedish population or purchased by less than 0.4% of men or women, respectively, were excluded to avoid random variation due to small numbers.

Crude and age adjusted values were calculated. Age standardisation was performed by direct standardisation, where the Swedish population on 31 December 2009 (4 649 014 men and 4 691 668 women[13]) was used as the standard population. In the calculations, 5-year age groups were used. Differences between the sexes were calculated as a risk ratio (RR) of women/men with 95% confidence intervals (CI). All analyses were performed in Microsoft Excel 2007 and SAS ver. 9.2 (SAS Institute, Cary, NC) using descriptive statistical methods.

Results

In 2010, the total volume of drugs sold in Sweden was 5.8 billion Defined Daily Doses (DDD), corresponding to 1715 DDD/1000 inhabitants daily. The total expenditures were 35.6 billion Swedish Kronor (SEK) (100 SEK = 8.96 GBP, September 2012). Drugs prescribed in ambulatory care, and thus included in the study, accounted for 88 % of the total volume and 72 % of the total expenditures on drugs in the country.

In all, 2.8 million men (59%) and 3.6 million women (76%), purchased at least one prescribed drug during 2010. The older the patient, the higher the likelihood of drug purchase. Women purchased more prescription drugs in all age groups except among children under the age of 10, even when hormonal contraceptives were excluded (Table 1).

Crude sex differences in prevalence were found in 48 of the 50 pharmacological ATC groups included (Figure 1, Table 2). After age adjustment, sex differences remained in 48 ATC groups. For antiglaucoma (S01E) and endocrine drugs (L02), the sex differences disappeared after age adjustment, while the opposite was seen for ARBs (angiotensin II receptor blockers) (C09C+D) and calcium channel blockers (C08), with a slightly higher utilisation in men after age adjustment. Beta blocking agents (C07) and cardiac glycosides (C01A) were more common in women before age adjustment, but were found to be more common in men after adjustment. The large differences in drugs for treatment of bone diseases (M05), thyroid therapy (H03), mineral supplements (A12) and anti-dementia drugs (N06D) diminished after age adjustment, even though the higher utilisation in women remained (Table 2).

The pharmacological groups with the largest relative differences with higher utilisation in women were antimycotics for systemic use (RR 6.6), drugs for osteoporosis (RR 4.9) and

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thyroid therapy (RR 4.5), while the utilisation was higher in men for antigout preparations (RR 0.4), psychostimulants (0.6) and ACE-inhibitors (RR 0.7) (Figure 2).

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The largest sex difference in absolute numbers was found for systemic antibacterials (J01) that were more common in women, 265.5 patients exposed (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (H03), purchased by 65.7 PAT/1000 women and 13.1 PAT/1000 men, and antidepressants (N06A), purchased by 106.6 PAT/1000 women and 55.4 PAT/1000 men.

The incidence showed a similar pattern as the prevalence (Table 3). However, the sex differences were substantially higher for endocrine therapy (L02) and urinary antispasmodic agents (G04BD). Before age adjustment, 40 pharmacological groups were more frequently dispensed to women and eight groups to men. After age adjustment, sex differences remained in 36 and 11 ATC-groups for women and men, respectively. In only one pharmacological group, drugs for treatment of bone diseases (M05), the sex difference diminished substantially after age adjustment.

Discussion

This drug utilisation study shows substantial sex differences in purchases of prescription drugs in Sweden. It is obvious that some of these differences may be explained by variations in disease prevalence, severity of disease, pathophysiology, diagnostics and treatment response or by other biologic differences such as those induced by pregnancy and/or lactation. However, it is also evident that other differences lack a rational medical explanation.

Throughout their lifespan, women have more contact with the health care system, which provides them with an extra opportunity for detection of disease. In the pre-menopausal years, a woman's need for contraceptives, pregnancy and childbirth and, in the peri- and postmenopausal period, screening programs for breast and cervical cancers and gynecological disorders require health care consultations.[16] Also, chronic disabling diseases associated with a chronic need for medication, such as musculoskeletal disorders, are more common in women than men.[17] From a gender perspective, studies have shown that men are less prone to seek preventive health care.[18]

Some differences between the sexes were expected. The higher utilisation of antimycotics in women could partly be explained by gynecological infections such as vaginitis. Also, the 4.5 times higher utilisation of thyroid therapy corresponds to a four times higher prevalence of impaired thyroid function in women.[19] The sex difference in utilisation of anti migraine drugs could be explained by a two to three times higher prevalence of migraine among women.[20] Men purchased more psychostimulants, corresponding well to a higher prevalence of ADHD[21] and autism[22].

A large sex difference was observed for antibiotics. Men are more susceptible to infections than women in general, yet we found a higher absolute utilisation of antibiotics in women. A common reason for prescribing antibiotics in primary care is urinary tract infection (UTI), which is much more prevalent in women.[23] An overdiagnosis of this condition in women has, however, been reported, which could potentially explain some of the higher utilisation in women.[24] Women were dispensed more anti-obesity drugs than men in spite of obesity being more common in men.[25 26] Also, more women than men undergo obesity surgery.[27] There are reasons to believe that the sociocultural pressure for women to be slim is higher than for men which could explain this prescription pattern.

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In the cardiovascular field several differences in utilisation of prescribed drugs were found. ACE inhibitors, primarily used for the treatment of heart failure and hypertension with the same prevalence in both sexes, were purchased by men to a larger extent. This may be due to the higher frequency of coughing as an adverse event in women.[28] However, the alternative treatment ARB was purchased by women and men to the same extent. Our findings may therefore indicate an under-use of renin-angiotensin-agents in women. Lipid lowering drugs were also purchased more frequently by men. The higher utilisation may be explained by the higher prevalence of ischemic heart disease (IHD). However, studies have shown that these drugs are under-used for secondary prevention in women[29-32]. Reasons for this could be that women suffer more from myalgia as an adverse reaction[33] but also that women are older and have more co-morbidity when suffering from cardiovascular disease, thus receiving less intensive secondary preventive medication.

Men were dispensed more anticoagulants. The most common indication for anticoagulants is atrial fibrillation, a condition more commonly found in men but carrying a higher risk of fatal complications like embolic stroke, for women.[34] Under-utilisation of anticoagulants in women with atrial fibrillation has been shown in earlier studies.[29 32 35-38] Men were also dispensed anti-arrhythmic drugs to a higher degree than women. This may be appropriate as women have a higher risk of the fatal arrhythmia “torsade de pointe-ventricular tachycardia” induced by some anti-arrhythmics like sotalol and quinidine.[39]

The main strength of this study is the complete coverage of all dispensed prescription drugs to the entire Swedish population. This provides a population-based overview of drug utilisation difficult to acquire in many other health systems. Furthermore, data on dispensed drugs is closer to the actual consumption than data on prescribed drugs, and it is free from recall bias common in patient reported data.[40]

The most important limitation is the lack of information on patient characteristics and clinical data to assess the rationale behind the observed differences. Furthermore, it is important to emphasise that gender differences may only be hypothesised from these data.

In conclusion, in this large study we found substantial differences in drug utilisation between men and women. In an attempt to explain these sex differences we searched the literature. Some sex disparities could be explained by differences in prevalence of disease or frequency of adverse reactions. Less medically justified explanations were also identified such as overestimation of risk vs. benefit in women compared to men. We also found suggestions that gender aspects such as societal acceptance of overweight in women compared to men may be involved. More research and a greater awareness of the influence of sex- and gender in health and disease are needed to ensure rational drug use in both men and women.

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Contributors: KSG proposed the study. All authors developed the study design. DL conducted the analyses. All authors contributed to interpreting the data and drafting the manuscript.

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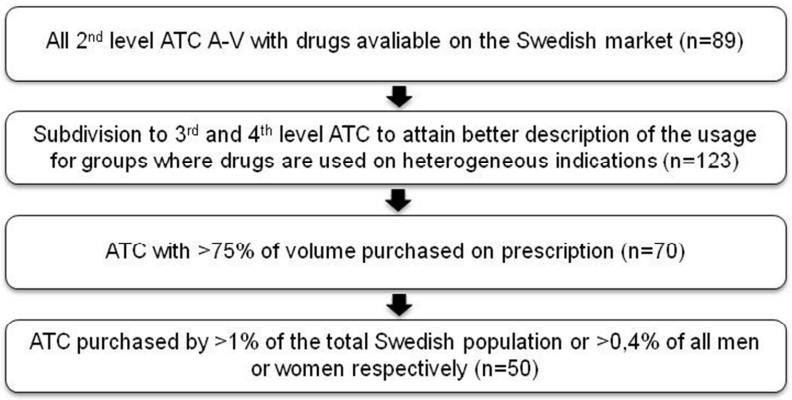
Ethical approval: The study was approved by the regional Ethics Committee at Karolinska Institutet, Sweden. Ref. no. 2010/788-31/5.

Data sharing: Proposals for data sharing should be sent to the corresponding author.

Figure 1. Flow chart showing the selection of pharmacological groups included in the specific analyses on sex- and gender differences in different therapeutic areas.



[1] Cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06) and ophthalmologicals (S01)

[2] Volume was measured in Defined Daily Doses (DDDs), except for eight ATC groups without any assigned DDD values where packages were used instead.

Figure 2. Pharmacological groups with the highest age adjusted relative differences in prevalence 2010.

ATC	Pharmacological group	PAT/TIN	
		Men	Women
J02	Antimycotics for systemic use	2.8	18.9
M05	Drugs for treatment of bone diseases	3.2	19.3
H03	Thyroid therapy	13.1	65.7
N02C	Antimigraine preparations	5.0	17.2
A12	Mineral supplements	16.2	57.3
A08	Antiobesity preparations	1.6	4.1
J05	Antivirals for systemic use	7.9	14.8
P01	Antiprotozoals	11.0	20.6
N06A	Antidepressants	55.4	106.6
H01	Pituitary and hypothalamic hormones	2.5	4.1
C09C+D	Angiotensin II antagonists and comb.	45.2	46.6
C08	Calcium channel blockers	60.8	59.6
C01A	Cardiac glycosides	6.0	6.8
C10	Lipid modifying agents	98.0	81.1
C01D	Vasodilators used in cardiac diseases	24.9	23.6
B01	Antithrombotic agents	109.8	97.7
A10	Drugs used in diabetes	45.3	34.5
C09A+B	ACE inhibitors and combinations	78.1	60.9
N06B	Psychostimulants	6.9	4.1
M04	Antigout preparations	12.2	5.9

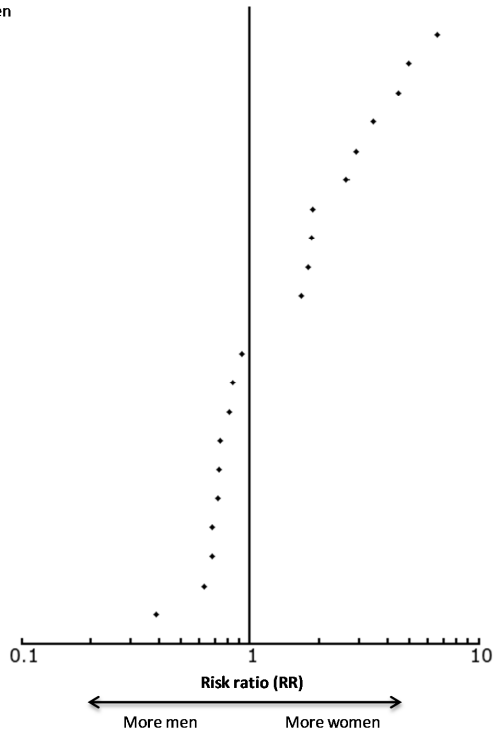


Table 1. Proportions of the Swedish population purchasing at least one prescribed drug in 2010, by age and sex.

Age group	Men (%)	Women (%)	Women excl. hormonal contraceptives (G03A) (%)
0- 4	68	64	64
5- 9	45	43	43
10-14	39	45	44
15-19	42	77	62
20-24	39	77	60
25-29	42	74	62
30-34	46	73	65
35-39	50	73	66
40-44	53	73	67
45-49	58	74	71
50-54	64	78	77
55-59	72	82	82
60-64	79	85	85
65-69	84	88	88
70-74	89	92	92
75-79	93	94	94
80-84	95	96	96
85-89	96	96	96
90 +	97	99	99
Total	*59*	*76*	*71*

Table II. Sex differences in prevalence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/TIN = number of patients (men or women) per 1000 individuals. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/TIN		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.75	18.90	6.87 (6.74-7.00)	6.56 (6.44-6.68)
M05	Drugs for treatment of bone diseases	3.19	19.28	6.04 (5.94-6.14)	4.95 (4.87-5.03)
H03	Thyroid therapy	13.12	65.67	5.00 (4.96-5.05)	4.46 (4.42-4.50)
N02C	Antimigraine Preparations	5.03	17.24	3.43 (3.38-3.48)	3.44 (3.39-3.49)
A12	Mineral supplements	16.19	57.29	3.54 (3.51-3.57)	2.90 (2.88-2.92)
A08	Antiobesity preparations	1.59	4.13	2.60 (2.53-2.67)	2.62 (2.55-2.69)
J05	Antivirals for systemic use	7.85	14.79	1.88 (1.86-1.91)	1.86 (1.84-1.89)
P01	Antiprotozoals	11.00	20.55	1.87 (1.85-1.89)	1.85 (1.83-1.87)
N06A	Antidepressants	55.35	106.60	1.93 (1.92-1.93)	1.79 (1.78-1.80)
H01	Pituitary and hypothalamic hormones and analogues	2.46	4.08	1.66 (1.62-1.70)	1.66 (1.63-1.70)
N05B	Anxiolytics	39.39	70.01	1.78 (1.77-1.79)	1.60 (1.59-1.61)
N05C	Hypnotics and sedatives	58.35	103.83	1.78 (1.77-1.79)	1.56 (1.56-1.57)
M03	Muscle relaxants	6.38	9.98	1.56 (1.54-1.59)	1.53 (1.51-1.56)
B03	Antianemic preparations	40.35	73.24	1.82 (1.81-1.83)	1.48 (1.47-1.49)
J01	Antibacterials for systemic use	191.26	265.58	1.39 (1.39-1.39)	1.36 (1.36-1.36)
L04	Immunosuppressants	7.32	10.05	1.37 (1.35-1.39)	1.33 (1.31-1.35)
G04BD	Urinary antispasmodics	6.12	9.61	1.57 (1.55-1.60)	1.33 (1.31-1.35)
A02	Drugs for acid related disorders	70.08	101.87	1.45 (1.45-1.46)	1.31 (1.31-1.32)
H02	Corticosteroids for systemic use	37.17	51.98	1.40 (1.39-1.41)	1.30 (1.30-1.31)
S01B	Anti-inflammatory agents	12.72	18.95	1.49 (1.47-1.50)	1.30 (1.29-1.31)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	13.77	19.35	1.40 (1.39-1.42)	1.29 (1.28-1.30)
N02A	Opioids	66.90	92.97	1.39 (1.38-1.40)	1.27 (1.27-1.28)
C03	Diuretics	59.48	92.83	1.56 (1.55-1.57)	1.24 (1.24-1.25)
S02	Otologicals	4.54	5.71	1.26 (1.24-1.28)	1.23 (1.21-1.25)
R03	Drugs for obstructive airway diseases	71.79	88.80	1.24 (1.23-1.24)	1.20 (1.20-1.21)
S03	Ophthalmological and otological preparations	23.31	28.38	1.22 (1.21-1.23)	1.18 (1.17-1.19)

N03	Antiepileptics	18.22	22.08	1.21 (1.20-1.22)	1.15 (1.14-1.16)
N05A	Antipsychotics	13.59	16.51	1.21 (1.20-1.23)	1.11 (1.09-1.12)
N06D	Anti-dementia drugs	3.38	5.41	1.60 (1.57-1.63)	1.10 (1.07-1.12)
N04	Anti-parkinson drugs	6.83	8.49	1.24 (1.22-1.26)	1.06 (1.05-1.08)
S01E	Antiglaucoma preparations and miotics	13.57	18.49	1.36 (1.35-1.38)	1.02 (1.01-1.03)
L02	Endocrine therapy	6.34	7.60	1.20 (1.18-1.22)	0.96 (0.95-0.97)
C07	Beta blocking agents	97.82	107.57	1.10 (1.10-1.10)	0.94 (0.93-0.94)
C09C+D	Angiotensin II antagonists and combinations	45.16	46.56	1.03 (1.02-1.04)	0.91 (0.91-0.92)
C08	Calcium channel blockers	60.84	59.61	0.98 (0.97-0.98)	0.84 (0.84-0.84)
C01A	Cardiac glycosides	6.01	6.83	1.14 (1.12-1.16)	0.81 (0.79-0.82)
C10	Lipid modifying agents	98.03	81.05	0.83 (0.82-0.83)	0.74 (0.73-0.74)
C01D	Vasodilators used in cardiac diseases	24.94	23.61	0.95 (0.94-0.95)	0.73 (0.72-0.73)
B01	Antithrombotic agents	109.81	97.68	0.89 (0.89-0.89)	0.72 (0.72-0.73)
A10	Drugs used in diabetes	45.27	34.48	0.76 (0.76-0.77)	0.68 (0.68-0.69)
C09A+B	ACE-inhibitors and combinations	78.14	60.90	0.78 (0.78-0.78)	0.68 (0.67-0.68)
N06B	Psychostimulants	6.94	4.11	0.59 (0.58-0.60)	0.62 (0.61-0.64)
M04	Antigout preparations	12.24	5.91	0.48 (0.48-0.49)	0.38 (0.38-0.39)

*The following pharmacological groups are not presented in the table due to sex-specific indications; G02 Other gynecologicals (dispensed to 9.79 PAT/1000 women and 0.20 PAT/1000 men), G03A Hormonal contraceptives (dispensed to 132.05 PAT/1000 women and 0.08 PAT/1000 men), G03C Estrogens (dispensed to 69.62 PAT/1000 women and 0.08 PAT/1000 men), G03D Progestogens (dispensed to 15.90 PAT/1000 women and 0.03 PAT/1000 men), G03F Progestogens and estrogens in combination (dispensed to 12.26 PAT/1000 women and 0.00 PAT/1000 men), G04C Drugs used in benign prostatic hypertrophy (dispensed to 0.25 PAT/1000 women and 26.23 PAT/1000 men) and G04BE Drugs used in erectile dysfunction (dispensed to 25.38 PAT/1000 men and 0.07 PAT/1000 women).

Table III. **Sex differences in incidence of drug therapy in Sweden 2010 by pharmacological group.** Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/1000 PYs = number of patients (men or women) per 1000 patient-years. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/1000 PYs		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.28	13.23	5.80 (5.68-5.92)	5.49 (5.38-5.60)
H03	Thyroid therapy	1.55	5.77	3.72 (3.62-3.81)	3.49 (3.40-3.58)
M05	Drugs for treatment of bone diseases	0.97	3.98	4.11 (3.98-4.24)	3.49 (3.38-3.60)
N02C	Antimigraine Preparations	1.89	4.99	2.64 (2.57-2.70)	2.67 (2.61-2.74)
A08	Antiobesity preparations	0.55	1.41	2.57 (2.45-2.69)	2.60 (2.48-2.72)
H01	Pituitary and hypothalamic hormones and analogues	0.99	2.45	2.47 (2.38-2.55)	2.48 (2.40-2.57)
A12	Mineral supplements	5.82	14.85	2.55 (2.52-2.59)	2.21 (2.18-2.24)
J05	Antivirals for systemic use	4.60	8.53	1.85 (1.82-1.89)	1.80 (1.77-1.83)
P01	Antiprotozoals	9.38	16.83	1.80 (1.77-1.82)	1.79 (1.76-1.81)
B03	Antianemic preparations	12.28	23.72	1.93 (1.91-1.95)	1.70 (1.68-1.72)
N06A	Antidepressants	15.35	24.71	1.61 (1.59-1.62)	1.52 (1.51-1.54)
L02	Endocrine therapy	1.37	2.43	1.78 (1.73-1.84)	1.52 (1.48-1.56)
N05B	Anxiolytics	17.90	28.41	1.59 (1.57-1.60)	1.47 (1.46-1.48)
M03	Muscle relaxants	4.50	6.67	1.48 (1.46-1.51)	1.46 (1.44-1.49)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	6.68	10.27	1.39 (1.37-1.41)	1.39 (1.37-1.41)
A02	Drugs for acid related disorders	25.47	37.35	1.47 (1.46-1.48)	1.38 (1.37-1.39)
N05C	Hypnotics and sedatives	18.90	26.94	1.43 (1.41-1.44)	1.32 (1.31-1.34)
S01B	Anti-inflammatory agents	9.27	13.71	1.48 (1.46-1.50)	1.29 (1.27-1.31)
H02	Corticosteroids for systemic use	21.36	28.28	1.32 (1.31-1.33)	1.27 (1.26-1.28)
N03	Antiepileptics	4.76	6.29	1.32 (1.30-1.35)	1.25 (1.22-1.27)
L04	Immunosuppressants	1.43	1.80	1.26 (1.22-1.30)	1.23 (1.20-1.27)
J01	Antibacterials for systemic use	126.14	153.73	1.22 (1.21-1.22)	1.21 (1.20-1.21)
R03	Drugs for obstructive airway diseases	27.19	32.11	1.18 (1.17-1.19)	1.19 (1.18-1.20)
N04	Anti-parkinson drugs	1.67	2.26	1.35 (1.31-1.39)	1.19 (1.15-1.22)
S02	Otologicals	3.39	4.04	1.19 (1.17-1.22)	1.17 (1.14-1.19)

N02A	Opioids	39.55	48.30	1.22 (1.21-1.23)	1.14 (1.14-1.15)
C03	Diuretics	10.63	14.35	1.35 (1.33-1.37)	1.14 (1.13-1.15)
S03	Ophthalmological and otological preparations	18.43	21.41	1.16 (1.15-1.17)	1.14 (1.13-1.15)
G04BD	Urinary antispasmodics	2.63	3.33	1.27 (1.24-1.30)	1.10 (1.08-1.13)
N05A	Antipsychotics	3.27	4.03	1.23 (1.21-1.26)	1.07 (1.05-1.10)
N06D	Anti-dementia drugs	0.91	1.38	1.52 (1.46-1.58)	1.07 (1.03-1.11)
B01	Antithrombotic agents	15.05	17.48	1.16. (1.15-1.7)	1.05 (1.04-1.06)
C07	Beta blocking agents	12.16	13.61	1.12 (1.11-1.13)	1.02 (1.01-1.03)
S01E	Antiglaucoma preparations and miotics	1.90	2.15	1.13 (1.10-1.16)	0.96 (0.93-0.98)
C09C+D	Angiotensin II antagonists and combinations	6.18	6.42	1.04 (1.02-1.05)	0.95 (0.93-0.96)
C08	Calcium channel blockers	10.35	10.72	1.04 (1.02-1.05)	0.93 (0.92-0.94)
C01A	Cardiac glycosides	1.09	1.24	1.14 (1.10-1.18)	0.86 (0.82-0.89)
C09A+B	ACE-inhibitors and combinations	14.28	13.11	0.92 (0.91-0.93)	0.83 (0.82-0.84)
C10	Lipid modifying agents	13.01	11.28	0.87 (0.86-0.88)	0.81 (0.80-0.82)
A10	Drugs used in diabetes	4.83	3.79	0.79 (0.77-0.80)	0.73 (0.72-0.75)
N06B	Psychostimulants	2.36	1.57	0.67 (0.65-0.69)	0.70 (0.68-0.72)
C01D	Vasodilators used in cardiac diseases	8.34	6.93	0.83 (0.82-0.84)	0.69 (0.68-0.70)
M04	Antigout preparations	2.71	1.44	0.53 (0.51-0.55)	0.44 (0.42-0.45)

*The following pharmacological groups were excluded from the table due to sex-specific indications; G02 Other gynecologicals (dispensed to 5.33 PAT/1000 PYs in women and 0.03 PAT/1000 PYs in men), G03A Hormonal contraceptives (dispensed to 42.09 PAT/1000 PYs in women and 0.04 PAT/1000 PYs in men), G03C Estrogens (dispensed to 16.44 PAT/1000 PYs in women and 0.03 PAT/1000 PYs in men), G03D Progestogens (dispensed to 11.20 PAT/1000 PYs in women and 0.01 PAT/1000 PYs in men), G03F Progestogens and estrogens in combination (dispensed to 2.56 PAT/1000 PYs in women and 0.00 PAT/1000 PYs in men), G04C Drugs used in benign prostatic hypertrophy (dispensed to 0.20 PAT/1000 PYs in women and 7.34 PAT/1000 PYs in men) and G04BE Drugs used in erectile dysfunction (dispensed to 0.03 PAT/1000 PYs in women and 10.16 PAT/1000 PYs in men).

Article Summary

Article focus

- To analyse drug utilisation in a whole country
- To identify areas of potential discrepancies in drug utilisation patterns between men and women
- To review existing literature for explanations for differences in drug utilisation between men and women
- To raise awareness about differences in drug utilisation between men and women which may not be rational

Key messages'

- Differences in drug utilisation between men and women in both prevalence and incidence were found in Sweden overall, and for 48 of 50 pharmacological groups.
- Many sex differences in drug utilisation in our study may be explained by sex differences in morbidity or biology. Other differences are hard to explain on medical grounds and may indicate unequal treatment.
- There are few studies analysing the rational of the observed sex differences.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	na

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	na
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	na
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	na
		Cross-sectional study—Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table 1. Proportions of the Swedish population purchasing at least one prescribed drug in 2010 by age and sex.

Age group	Men (%)	Women (%)	Women excl. hormonal contraceptives (G03A) (%)
0- 4	68	64	64
5- 9	45	43	43
10-14	39	45	44
15-19	42	77	62
20-24	39	77	60
25-29	42	74	62
30-34	46	73	65
35-39	50	73	66
40-44	53	73	67
45-49	58	74	71
50-54	64	78	77
55-59	72	82	82
60-64	79	85	85
65-69	84	88	88
70-74	89	92	92
75-79	93	94	94
80-84	95	96	96
85-89	96	96	96
90 +	97	99	99
Total	*59*	*76*	*71*

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Differences in drug utilisation between men and women - a cross sectional analysis of all dispensed drugs in Sweden

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Title:

Differences in drug utilisation between men and women - a cross sectional analysis of all dispensed drugs in Sweden

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Article Summary

Article focus

- To use drug dispensing data to analyse drug utilisation in men and women in a whole country
- To identify areas of potential discrepancies in drugs dispensed to men and women
- To review existing literature for explanations for differences in drug use between men and women
- To raise awareness about differences in drug use between men and women which may not be rational

Key messages'

- Differences in men and women in the prevalence and incidence of dispensed drugs were found in Sweden overall, and for 48 of 50 pharmacological groups.
- Many sex differences found in our study may be explained by sex differences in morbidity or biology. Other differences are hard to explain on medical grounds and may indicate unequal treatment.
- There are few studies analysing the rational of the observed sex differences.

Abstract

Objectives: Ascertain the extent of differences between men and women in dispensed drugs since there is a lack of comprehensive overviews on sex differences in the use of prescription drugs.

Design: Cross-sectional population database analysis

Methods: Data on all dispensed drugs in 2010 to the entire Swedish population (9.3 million inhabitants) were obtained from the Swedish Prescribed Drug Register. All pharmacological groups with ambulatory care prescribing accounting for >75% of the total volume in Defined Daily Doses (DDDs) and a prevalence of >1% were included in the analysis. Crude and age adjusted difference in prevalence and incidence were calculated as risk ratios (RR) of women/men.

Results: In all, 2.8 million men (59%) and 3.6 million women (76%) were dispensed at least one prescribed drug during 2010. Women were dispensed more drugs in all age groups except among children under the age of 10. The largest sex difference in prevalence in absolute numbers was found for antibiotics that were more common in women, 265.5 patients (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (65.7 PAT/1000 women and 13.1 PAT/1000 men), and antidepressants (106.6 PAT/1000 women and 55.4 PAT/1000 men). Age adjusted relative sex differences in prevalence were found in 48 of the 50 identified pharmacological groups. The pharmacological groups with the largest relative differences of dispensed drugs were systemic antimycotics (RR 6.6 CI 6.4-6.7), drugs for osteoporosis (RR 4.9 CI 4.9-5.0) and thyroid therapy (RR 4.5 CI 4.4-4.5) which were dispensed to women to a higher degree. Antigout agents (RR 0.4 CI 0.4-0.4), psychostimulants (RR 0.6 CI 0.6-0.6) and ACE inhibitors (RR 0.7 CI 0.7-0.7) were dispensed to men to a larger proportion.

Conclusion: Substantial differences in the prevalence and incidence of dispensed drugs were found between men and women. Some differences may be rational and desirable related to differences between the sexes in incidence or prevalence of disease or by biologic differences. Other differences are more difficult to explain on medical grounds and may indicate unequal treatment.

Introduction

Drug therapy plays an important role in preserving people's health and improving their quality of life. Consequently, drugs are the most important treatment options for most diseases and the majority of medical consultations result in a prescription.[1] Furthermore, pharmaceuticals also constitute a significant proportion of healthcare spending, more rapidly increasing than other healthcare components in many countries.[2 3] In Sweden, pharmaceuticals accounted for 12.6 % of the total health care expenditure in 2010[4], but the growth has been moderated after the implementation of major reforms.[5]

Rational drug use implies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community".[6] Individual requirements indicate that not only severity of disease, co-morbidity, renal function and age should be considered, but also sex and gender. While it is evident that biological differences, commonly referred to as "sex differences", should be considered when prescribing medicines, it is unclear to what extent socio-cultural differences, commonly referred to as "gender differences" should be considered by the prescribing physician. Sex differences in drug use have been demonstrated in several therapeutic areas.[7-11] However, there is a lack of both comprehensive overviews on sex- and gender differences of drug use in entire populations and especially studies analysing the rationale behind the observed differences. Variations in morbidity may explain some differences, whereas other differences may indicate inequities and under- or overuse of certain drugs in men or women.

WHO defines "drug utilisation" as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the medical, social, and economic consequences".[12] Drug utilisation data can be derived from different levels in the medication use process; sales

data from the manufacturers to wholesalers, the dispensing data at pharmacies, or patient consumption surveys.[13 14] The use of dispensed prescriptions as a measure of drug exposure has many advantages since it eliminates recall bias and improves the accuracy of the information on the drug use.[13 15] In 2005, a national registry on dispensed drugs to the entre Swedish population was established.[16] It contains complete data (>99 % coverage) with unique identifiers of all prescribed drugs dispensed to the entire Swedish population of 9.3 million inhabitants, and may offer a good opportunity to study sex and gender differences in drug use.

The aim of this study was to describe and analyse differences in prevalence and incidence between men and woman of drugs dispensed to the Swedish population. The findings may subsequently be used to plan future studies to address differences suggesting inequity in treatment approaches.

Methods

This was a cross-sectional study analysing sex differences in prevalence and incidence of drugs dispensed in ambulatory care in Sweden in 2010, overall and within different pharmacological groups. Data were collected from the Swedish Prescribed Drug Register (SPDR).[16]

The period prevalence was defined as the proportion of the population in the country dispensed ≥1 prescription in 2010 and measured in number of patients exposed per 1000 inhabitants (PAT/TIN). Incidence was defined as the proportion of the population having at least one prescription dispensed in a pharmacy in 2010 after a one-year wash-out period with no drug dispensed and was measured in number of patients per 1000 person-years (PAT/1000 PYs).

Pharmacological groups were selected by using the following procedure:

1. All 89 Anatomical Therapeutic Chemical (ATC) 2nd level groups with drugs available on the Swedish market[17 18] were identified.
2. In large ATC groups and ATC groups with drugs used for multiple heterogeneous indications, i.e. cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06), ophthalmologicals (S01), a subdivision was done to ATC 3rd or 4th level to attain a more clinically relevant description of the utilisation.
3. ATC groups with less than 75% of the total sales volume in the country purchased on prescription were excluded since sex distribution was not possible to collect for those purchased over-the-counter (OTC) or used in inpatient care. Volume was measured in the technical unit numbers of Defined Daily Doses (DDDs), except for eight pharmacological groups for which there were no DDDs assigned.[18] For these groups, packages were used as volume measure. Calculations of the proportion of the total volume dispensed as prescriptions in ambulatory care were based on aggregated volume data from all Swedish pharmacies.
4. For the identified ATC groups at various hierarchical levels, groups that were dispensed to less than 1% of the total Swedish population or dispensed to less than 0.4% of men or women, respectively, were excluded to avoid random variation due to small numbers.

Crude and age adjusted values were calculated. Age standardisation was performed by direct standardisation, where the Swedish population on 31 December 2009 (4 649 014 men and 4 691 668 women[19]) was used as the standard population. In the calculations, 5-year age

groups were used. Differences between the sexes were calculated as a risk ratio (RR) of women/men with 95% confidence intervals (CI). All analyses were performed in Microsoft Excel 2007 and SAS ver. 9.2 (SAS Institute, Cary, NC) using descriptive statistical methods.

Results

In 2010, the total volume of drugs dispensed in Sweden was 5.8 billion Defined Daily Doses (DDD), corresponding to 1715 DDD/1000 inhabitants daily. The total expenditures were 35.6 billion Swedish Kronor (SEK) (100 SEK = 8.96 GBP, September 2012). Drugs prescribed in ambulatory care, and thus included in the study, accounted for 88 % of the total volume and 72 % of the total expenditures on drugs in the country.

In all, 2.8 million men (59%) and 3.6 million women (76%), were dispensed at least one prescribed drug during 2010. The older the patient, the higher the likelihood was of being dispensed drugs. Women were in general dispensed more prescription drugs in all age groups except among children under the age of 10, even when hormonal contraceptives were excluded (Table 1).

Crude sex differences in prevalence were found in 48 of the 50 pharmacological ATC groups included (Figure 1, Table 2). After age adjustment, sex differences remained in 48 ATC groups. Concerning drugs for glaucoma (S01E) and endocrine drugs (L02), the sex differences disappeared after age adjustment, while the opposite was seen for angiotensin receptor blockers (ARBs) (C09C+D) and calcium channel blockers (C08), that were more common in men after age adjustment. Beta blocking agents (C07) and cardiac glycosides (C01A) were more common in women before age adjustment, but were found to be more common in men after adjustment. The large differences in drugs for treatment of bone diseases such as osteoporosis (M05), thyroid therapy (H03), mineral supplements (A12) and anti-dementia drugs (N06D) diminished after age adjustment, even though they still were more common in women after adjustment (Table 2).

The pharmacological groups with the largest relative differences more commonly being dispensed to women were antimycotics for systemic use (RR 6.6), drugs for osteoporosis (RR 4.9) and thyroid therapy (RR 4.5), while a larger proportion of men were dispensed antigout preparations (RR 0.4), psychostimulants (0.6) and ACE-inhibitors (RR 0.7) (Figure 2).

The largest sex difference in absolute numbers was found for systemic antibacterials (J01) that were more common in women, 265.5 PAT/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (H03), 65.7 PAT/1000 women and 13.1 PAT/1000 men, and antidepressants (N06A), 106.6 PAT/1000 women and 55.4 PAT/1000 men.

The incidence showed a similar pattern as the prevalence (Table 3). However, the sex differences were substantially higher for endocrine therapy (L02) and urinary antispasmodic agents (G04BD). Before age adjustment, 40 pharmacological groups were more frequently dispensed to women and eight groups to men. After age adjustment, sex differences remained in 36 and 11 ATC-groups for women and men, respectively. In only one pharmacological group, drugs for treatment of bone diseases (M05), the sex difference diminished substantially after age adjustment.

Discussion

This study of all dispensed prescription drugs in Sweden shows substantial differences between men and women. It is obvious that some of these differences may be explained by variations in disease prevalence, severity of disease, pathophysiology, diagnostics and treatment response or by other biologic differences such as those induced by pregnancy and/or

lactation. However, it is also evident that other differences lack a rational medical explanation.

Throughout their lifespan, women have more contact with the health care system[20-22], which may provide them with an extra opportunity for detection of disease and receiving prescriptions. In the pre-menopausal years, a woman's need for contraceptives, pregnancy and childbirth and, in the peri- and postmenopausal period, screening programs for breast and cervical cancers and gynecological disorders require health care consultations.[22] Also, chronic disabling diseases associated with a chronic need for medication, such as musculoskeletal disorders, are more common in women than men.[20] From a gender perspective, studies have shown that men are less prone to seek preventive health care.[21]

Some differences between the sexes are expected. The higher proportion of women dispensed antimycotics could partly be explained by gynecological infections such as vaginitis. Also, the 4.5 times higher proportion of dispensed thyroid therapy corresponds to a four times higher prevalence of impaired thyroid function in women.[23] The sex difference in the proportion of dispensed drugs for migraine could be explained by a two to three times higher prevalence of migraine among women.[24] Men were dispensed more psychostimulants, corresponding to a higher prevalence of ADHD[25] and autism[26].

The largest sex difference in absolute numbers was observed for antibiotics, more commonly dispensed to women. A common reason for prescribing antibiotics in primary care is urinary tract infection (UTI), which is more prevalent in women.[27] An over diagnosis of this condition in women has, however, been reported, which could potentially explain some of the higher number of women dispensed these drugs.[28] Women were dispensed more anti-obesity drugs than men in spite of obesity being more common in men.[29 30] Also, more women than men

undergo obesity surgery.[31] There are reasons to believe that the sociocultural pressure to be slim is higher for women and studies have shown that women are more dissatisfied with their weight and their body than men.[32 33] This could explain the prescription pattern.

In the cardiovascular field, several differences in dispensing of prescribed drugs were found. ACE inhibitors, primarily used for the treatment of heart failure and hypertension with the same prevalence in both sexes, were more commonly dispensed to men. This may be due to the higher frequency of coughing as an adverse event in women.[34] However, the alternative treatment ARB was dispensed to women and men to the same extent. Our findings may therefore indicate an under-use of renin-angiotensin-agents in women. Lipid lowering drugs were also dispensed more frequently to men. The higher proportion in men may be explained by the higher prevalence of ischemic heart disease (IHD). However, studies have shown that these drugs are under-used for secondary prevention in women.[35-38] Reasons for this could be that women suffer more from myalgia as an adverse reaction[39] but also that women are older and have more co-morbidity when suffering from cardiovascular disease, thus receive less intensive secondary preventive medication.

Men were dispensed more anticoagulants. The most common indication for anticoagulants is atrial fibrillation, a condition more commonly found in men but carrying a higher risk of fatal complications like embolic stroke, for women.[40] Underuse of anticoagulants in women with atrial fibrillation has been shown in earlier studies.[37 38 41-44] Men were also dispensed anti-arrhythmic drugs to a higher degree than women. This may be appropriate as women have a higher risk of the fatal arrhythmia “torsade de pointe-ventricular tachycardia” induced by some anti-arrhythmics like sotalol and quinidine.[45]

The main strength of this study is the complete coverage of all dispensed prescription drugs to the entire Swedish population. This provides a population-based overview of drug use difficult to acquire in many other health systems.[15] Although, it is important to recognise that filling a prescription does not necessarily imply that the drugs are taken, we have no reason to believe that misclassification of drug use should be more prevalent in one sex. Furthermore, data on dispensed drugs is closer to the actual intake than data on prescribed drugs, and it is free from recall bias common in patient reported data.[46] The most important limitation is the lack of information on patient characteristics and clinical data to assess the rationale behind the observed differences. Moreover, it is important to emphasise that gender differences may only be hypothesised from these data.

In conclusion, in this large study we found substantial differences in drugs dispensed to men and women. In an attempt to explain these sex differences we searched the literature. Some sex disparities could be explained by differences in prevalence of disease or frequency of adverse reactions. Less medically justified explanations were also identified such as overestimation of risk vs. benefit in women compared to men. We also found suggestions that gender aspects such as societal acceptance of overweight in women compared to men may be involved. More research and a greater awareness of the influence of sex- and gender in health and disease are needed to ensure rational drug use in both men and women.

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Contributors: KSG proposed the study. All authors developed the study design. DL conducted the analyses. All authors contributed to interpreting the data and drafting the manuscript.

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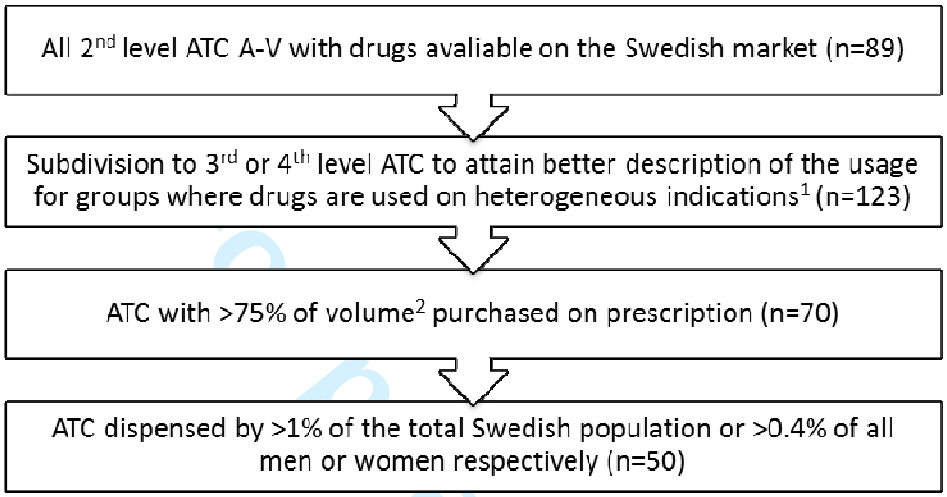
Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the regional Ethics Committee at Karolinska Institutet, Sweden. Ref. no. 2010/788-31/5.

Data sharing: Proposals for data sharing should be sent to the corresponding author.

Figure 1. Flow chart showing the selection of pharmacological groups included in the specific analyses on sex- and gender differences in different therapeutic areas.



[1] Cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06) and ophthalmologicals (S01)

[2] Volume was measured in Defined Daily Doses (DDDs), except for eight ATC groups without any assigned DDD values where packages were used instead.

Figure 2. Pharmacological groups with the highest age adjusted relative differences in prevalence 2010.

ATC	Pharmacological group	PAT/TIN	
		Men	Women
J02	Antimycotics for systemic use	2.8	18.9
M05	Drugs for treatment of bone diseases	3.2	19.3
H03	Thyroid therapy	13.1	65.7
N02C	Antimigraine preparations	5.0	17.2
A12	Mineral supplements	16.2	57.3
A08	Antiobesity preparations	1.6	4.1
J05	Antivirals for systemic use	7.9	14.8
P01	Antiprotozoals	11.0	20.6
N06A	Antidepressants	55.4	106.6
H01	Pituitary and hypothalamic hormones	2.5	4.1
C09C+D	Angiotensin II antagonists and comb.	45.2	46.6
C08	Calcium channel blockers	60.8	59.6
C01A	Cardiac glycosides	6.0	6.8
C10	Lipid modifying agents	98.0	81.1
C01D	Vasodilators used in cardiac diseases	24.9	23.6
B01	Antithrombotic agents	109.8	97.7
A10	Drugs used in diabetes	45.3	34.5
C09A+B	ACE inhibitors and combinations	78.1	60.9
N06B	Psychostimulants	6.9	4.1
M04	Antigout preparations	12.2	5.9

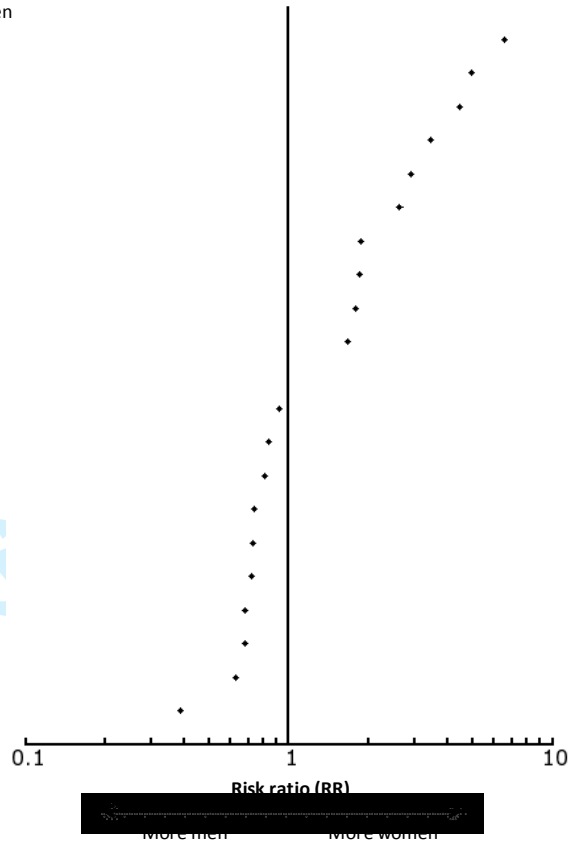


Table 1. Proportions of the Swedish population dispensed at least one prescribed drug in 2010, by age and sex.

Age group	Men (%)	Women (%)	Women excl. hormonal contraceptives (G03A) (%)
0- 4	68	64	64
5- 9	45	43	43
10-14	39	45	44
15-19	42	77	62
20-24	39	77	60
25-29	42	74	62
30-34	46	73	65
35-39	50	73	66
40-44	53	73	67
45-49	58	74	71
50-54	64	78	77
55-59	72	82	82
60-64	79	85	85
65-69	84	88	88
70-74	89	92	92
75-79	93	94	94
80-84	95	96	96
85-89	96	96	96
90 +	97	99	99
Total	*59*	*76*	*71*

Table II. Sex differences in prevalence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/TIN = number of patients (men or women) per 1000 individuals. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/TIN		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.75	18.90	6.87 (6.74-7.00)	6.56 (6.44-6.68)
M05	Drugs for treatment of bone diseases	3.19	19.28	6.04 (5.94-6.14)	4.95 (4.87-5.03)
H03	Thyroid therapy	13.12	65.67	5.00 (4.96-5.05)	4.46 (4.42-4.50)
N02C	Antimigraine Preparations	5.03	17.24	3.43 (3.38-3.48)	3.44 (3.39-3.49)
A12	Mineral supplements	16.19	57.29	3.54 (3.51-3.57)	2.90 (2.88-2.92)
A08	Antiobesity preparations	1.59	4.13	2.60 (2.53-2.67)	2.62 (2.55-2.69)
J05	Antivirals for systemic use	7.85	14.79	1.88 (1.86-1.91)	1.86 (1.84-1.89)
P01	Antiprotozoals	11.00	20.55	1.87 (1.85-1.89)	1.85 (1.83-1.87)
N06A	Antidepressants	55.35	106.60	1.93 (1.92-1.93)	1.79 (1.78-1.80)
H01	Pituitary and hypothalamic hormones and analogues	2.46	4.08	1.66 (1.62-1.70)	1.66 (1.63-1.70)
N05B	Anxiolytics	39.39	70.01	1.78 (1.77-1.79)	1.60 (1.59-1.61)
N05C	Hypnotics and sedatives	58.35	103.83	1.78 (1.77-1.79)	1.56 (1.56-1.57)
M03	Muscle relaxants	6.38	9.98	1.56 (1.54-1.59)	1.53 (1.51-1.56)
B03	Antianemic preparations	40.35	73.24	1.82 (1.81-1.83)	1.48 (1.47-1.49)
J01	Antibacterials for systemic use	191.26	265.58	1.39 (1.39-1.39)	1.36 (1.36-1.36)
L04	Immunosuppressants	7.32	10.05	1.37 (1.35-1.39)	1.33 (1.31-1.35)
G04BD	Urinary antispasmodics	6.12	9.61	1.57 (1.55-1.60)	1.33 (1.31-1.35)
A02	Drugs for acid related disorders	70.08	101.87	1.45 (1.45-1.46)	1.31 (1.31-1.32)
H02	Corticosteroids for systemic use	37.17	51.98	1.40 (1.39-1.41)	1.30 (1.30-1.31)
S01B	Anti-inflammatory agents	12.72	18.95	1.49 (1.47-1.50)	1.30 (1.29-1.31)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	13.77	19.35	1.40 (1.39-1.42)	1.29 (1.28-1.30)
N02A	Opioids	66.90	92.97	1.39 (1.38-1.40)	1.27 (1.27-1.28)
C03	Diuretics	59.48	92.83	1.56 (1.55-1.57)	1.24 (1.24-1.25)
S02	Otologicals	4.54	5.71	1.26 (1.24-1.28)	1.23 (1.21-1.25)

R03	Drugs for obstructive airway diseases	71.79	88.80	1.24 (1.23-1.24)	1.20 (1.20-1.21)
S03	Ophthalmological and otological preparations	23.31	28.38	1.22 (1.21-1.23)	1.18 (1.17-1.19)
N03	Antiepileptics	18.22	22.08	1.21 (1.20-1.22)	1.15 (1.14-1.16)
N05A	Antipsychotics	13.59	16.51	1.21 (1.20-1.23)	1.11 (1.09-1.12)
N06D	Anti-dementia drugs	3.38	5.41	1.60 (1.57-1.63)	1.10 (1.07-1.12)
N04	Anti-parkinson drugs	6.83	8.49	1.24 (1.22-1.26)	1.06 (1.05-1.08)
S01E	Antiglaucoma preparations and miotics	13.57	18.49	1.36 (1.35-1.38)	1.02 (1.01-1.03)
L02	Endocrine therapy	6.34	7.60	1.20 (1.18-1.22)	0.96 (0.95-0.97)
C07	Beta blocking agents	97.82	107.57	1.10 (1.10-1.10)	0.94 (0.93-0.94)
C09C+D	Angiotensin II antagonists and combinations	45.16	46.56	1.03 (1.02-1.04)	0.91 (0.91-0.92)
C08	Calcium channel blockers	60.84	59.61	0.98 (0.97-0.98)	0.84 (0.84-0.84)
C01A	Cardiac glycosides	6.01	6.83	1.14 (1.12-1.16)	0.81 (0.79-0.82)
C10	Lipid modifying agents	98.03	81.05	0.83 (0.82-0.83)	0.74 (0.73-0.74)
C01D	Vasodilators used in cardiac diseases	24.94	23.61	0.95 (0.94-0.95)	0.73 (0.72-0.73)
B01	Antithrombotic agents	109.81	97.68	0.89 (0.89-0.89)	0.72 (0.72-0.73)
A10	Drugs used in diabetes	45.27	34.48	0.76 (0.76-0.77)	0.68 (0.68-0.69)
C09A+B	ACE-inhibitors and combinations	78.14	60.90	0.78 (0.78-0.78)	0.68 (0.67-0.68)
N06B	Psychostimulants	6.94	4.11	0.59 (0.58-0.60)	0.62 (0.61-0.64)
M04	Antigout preparations	12.24	5.91	0.48 (0.48-0.49)	0.38 (0.38-0.39)

*The following pharmacological groups are not presented in the table due to sex-specific indications; G02 Other gynecologicals (dispensed to 9.79 PAT/1000 women and 0.20 PAT/1000 men), G03A Hormonal contraceptives (dispensed to 132.05 PAT/1000 women and 0.08 PAT/1000 men), G03C Estrogens (dispensed to 69.62 PAT/1000 women and 0.08 PAT/1000 men), G03D Progestogens (dispensed to 15.90 PAT/1000 women and 0.03 PAT/1000 men), G03F Progestogens and estrogens in combination (dispensed to 12.26 PAT/1000 women and 0.00 PAT/1000 men), G04C Drugs used in benign prostatic hypertrophy (dispensed to 0.25 PAT/1000 women and 26.23 PAT/1000 men) and G04BE Drugs used in erectile dysfunction (dispensed to 25.38 PAT/1000 men and 0.07 PAT/1000 women).

Table III. Sex differences in incidence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/1000 PYs = number of patients (men or women) per 1000 patient-years. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/1000 PYs		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.28	13.23	5.80 (5.68-5.92)	5.49 (5.38-5.60)
H03	Thyroid therapy	1.55	5.77	3.72 (3.62-3.81)	3.49 (3.40-3.58)
M05	Drugs for treatment of bone diseases	0.97	3.98	4.11 (3.98-4.24)	3.49 (3.38-3.60)
N02C	Antimigraine Preparations	1.89	4.99	2.64 (2.57-2.70)	2.67 (2.61-2.74)
A08	Antiobesity preparations	0.55	1.41	2.57 (2.45-2.69)	2.60 (2.48-2.72)
H01	Pituitary and hypothalamic hormones and analogues	0.99	2.45	2.47 (2.38-2.55)	2.48 (2.40-2.57)
A12	Mineral supplements	5.82	14.85	2.55 (2.52-2.59)	2.21 (2.18-2.24)
J05	Antivirals for systemic use	4.60	8.53	1.85 (1.82-1.89)	1.80 (1.77-1.83)
P01	Antiprotozoals	9.38	16.83	1.80 (1.77-1.82)	1.79 (1.76-1.81)
B03	Antianemic preparations	12.28	23.72	1.93 (1.91-1.95)	1.70 (1.68-1.72)
N06A	Antidepressants	15.35	24.71	1.61 (1.59-1.62)	1.52 (1.51-1.54)
L02	Endocrine therapy	1.37	2.43	1.78 (1.73-1.84)	1.52 (1.48-1.56)
N05B	Anxiolytics	17.90	28.41	1.59 (1.57-1.60)	1.47 (1.46-1.48)
M03	Muscle relaxants	4.50	6.67	1.48 (1.46-1.51)	1.46 (1.44-1.49)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	6.68	10.27	1.39 (1.37-1.41)	1.39 (1.37-1.41)
A02	Drugs for acid related disorders	25.47	37.35	1.47 (1.46-1.48)	1.38 (1.37-1.39)
N05C	Hypnotics and sedatives	18.90	26.94	1.43 (1.41-1.44)	1.32 (1.31-1.34)
S01B	Anti-inflammatory agents	9.27	13.71	1.48 (1.46-1.50)	1.29 (1.27-1.31)
H02	Corticosteroids for systemic use	21.36	28.28	1.32 (1.31-1.33)	1.27 (1.26-1.28)
N03	Antiepileptics	4.76	6.29	1.32 (1.30-1.35)	1.25 (1.22-1.27)
L04	Immunosuppressants	1.43	1.80	1.26 (1.22-1.30)	1.23 (1.20-1.27)
J01	Antibacterials for systemic use	126.14	153.73	1.22 (1.21-1.22)	1.21 (1.20-1.21)

R03	Drugs for obstructive airway diseases	27.19	32.11	1.18 (1.17-1.19)	1.19 (1.18-1.20)
N04	Anti-parkinson drugs	1.67	2.26	1.35 (1.31-1.39)	1.19 (1.15-1.22)
S02	Otologicals	3.39	4.04	1.19 (1.17-1.22)	1.17 (1.14-1.19)
N02A	Opioids	39.55	48.30	1.22 (1.21-1.23)	1.14 (1.14-1.15)
C03	Diuretics	10.63	14.35	1.35 (1.33-1.37)	1.14 (1.13-1.15)
S03	Ophthalmological and otological preparations	18.43	21.41	1.16 (1.15-1.17)	1.14 (1.13-1.15)
G04BD	Urinary antispasmodics	2.63	3.33	1.27 (1.24-1.30)	1.10 (1.08-1.13)
N05A	Antipsychotics	3.27	4.03	1.23 (1.21-1.26)	1.07 (1.05-1.10)
N06D	Anti-dementia drugs	0.91	1.38	1.52 (1.46-1.58)	1.07 (1.03-1.11)
B01	Antithrombotic agents	15.05	17.48	1.16. (1.15-1.7)	1.05 (1.04-1.06)
C07	Beta blocking agents	12.16	13.61	1.12 (1.11-1.13)	1.02 (1.01-1.03)
S01E	Antiglaucoma preparations and miotics	1.90	2.15	1.13 (1.10-1.16)	0.96 (0.93-0.98)
C09C+D	Angiotensin II antagonists and combinations	6.18	6.42	1.04 (1.02-1.05)	0.95 (0.93-0.96)
C08	Calcium channel blockers	10.35	10.72	1.04 (1.02-1.05)	0.93 (0.92-0.94)
C01A	Cardiac glycosides	1.09	1.24	1.14 (1.10-1.18)	0.86 (0.82-0.89)
C09A+B	ACE-inhibitors and combinations	14.28	13.11	0.92 (0.91-0.93)	0.83 (0.82-0.84)
C10	Lipid modifying agents	13.01	11.28	0.87 (0.86-0.88)	0.81 (0.80-0.82)
A10	Drugs used in diabetes	4.83	3.79	0.79 (0.77-0.80)	0.73 (0.72-0.75)
N06B	Psychostimulants	2.36	1.57	0.67 (0.65-0.69)	0.70 (0.68-0.72)
C01D	Vasodilators used in cardiac diseases	8.34	6.93	0.83 (0.82-0.84)	0.69 (0.68-0.70)
M04	Antigout preparations	2.71	1.44	0.53 (0.51-0.55)	0.44 (0.42-0.45)

*The following pharmacological groups were excluded from the table due to sex-specific indications; G02 Other gynecologicals (dispensed to 5.33 PAT/1000 PYs in women and 0.03 PAT/1000 PYs in men), G03A Hormonal contraceptives (dispensed to 42.09 PAT/1000 PYs in women and 0.04 PAT/1000 PYs in men), G03C Estrogens (dispensed to 16.44 PAT/1000 PYs in women and 0.03 PAT/1000 PYs in men), G03D Progestogens (dispensed to 11.20 PAT/1000 PYs in women and 0.01 PAT/1000 PYs in men), G03F Progestogens and estrogens in combination (dispensed to 2.56 PAT/1000 PYs in women and 0.00 PAT/1000 PYs in men), G04C Drugs used in benign prostatic hypertrophy (dispensed to 0.20 PAT/1000 PYs in women and 7.34 PAT/1000 PYs in men) and G04BE Drugs used in erectile dysfunction (dispensed to 0.03 PAT/1000 PYs in women and 10.16 PAT/1000 PYs in men).

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	na

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	na
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	na
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	na
		Cross-sectional study—Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Title:

Differences ~~in drug utilisation~~ between men and women - a cross sectional analysis of all dispensed drugs in Sweden

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Abstract

Objectives: Ascertain the extent of differences between men and women in dispensed drugs since there is a lack of comprehensive overviews on sex differences in ~~drug utilisation~~the use of prescription drugs.~~.~~

Design: Cross-sectional population database analysis

Methods: Data on all dispensed drugs in 2010 to the entire Swedish population (9.3 million inhabitants) were obtained from the Swedish Prescribed Drug Register. All pharmacological groups with ambulatory care prescribing accounting for >75% of the total volume in Defined Daily Doses (DDDs) and a prevalence of >1% were included in the analysis. Crude and age adjusted difference in prevalence and incidence were calculated as risk ratios (RR) of women/men.

Results: In all, 2.8 million men (59%) and 3.6 million women (76%)~~,~~ were dispensed at least one prescribed drug during 2010. Women were dispensed more ~~prescription~~ drugs in all age groups except among children under the age of 10. The largest sex difference in prevalence in absolute numbers was found for antibiotics that were more common in women, 265.5 patients (PAT)/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (65.7 PAT/1000 women and 13.1 PAT/1000 men), and antidepressants (106.6 PAT/1000 women and 55.4 PAT/1000 men). Age adjusted relative sex differences in prevalence were found in 48 of the 50 identified pharmacological groups. The pharmacological groups with the largest relative differences of dispensed drugs ~~with higher utilisation in women~~ were systemic antimycotics ~~-~~(RR 6.6 CI 6.4-6.7), drugs for osteoporosis (RR 4.9 CI 4.9-5.0) and thyroid ~~function~~ therapy (RR 4.5 CI 4.4-4.5)~~,~~ which were dispensed to women to a higher degree.~~while in men the utilisation was higher for~~ Antigout agents (RR

0.4 CI 0.4-0.4), psychostimulants (RR 0.6 CI 0.6-0.6) and ACE inhibitors (RR 0.7 CI 0.7-0.7) were dispensed to men to a larger proportion.

Conclusion: Substantial differences in the prevalence and incidence of dispensed drugs ~~utilisation~~ were found between men and women. Some differences may be rational and desirable related to differences between the sexes in incidence or prevalence of disease or by biologic differences. Other differences are more difficult to explain on medical grounds and may indicate unequal treatment.

Introduction

Drug therapy plays an important role in preserving people's health and improving their quality of life. Consequently, drugs are the most important treatment options for most diseases and the majority of medical consultations result in a prescription.[1] Furthermore, pharmaceuticals also constitute a significant proportion of healthcare spending, more rapidly increasing than other healthcare components in many countries.[2 3] In Sweden, pharmaceuticals accounted for 12.6 % of the total health care expenditure in 2010[4], but the growth has been moderated after the implementation of major reforms.[5]

Rational drug use implies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community".[6] Individual requirements indicate that not only severity of disease, co-morbidity, renal function and age should be considered, but also sex and gender. While it is evident that biological differences, commonly referred to as "sex differences", should be considered when prescribing medicines, it is unclear to what extent socio-cultural differences, commonly referred to as "gender differences" should be considered by the prescribing physician. Sex differences in drug ~~utilisation~~ use have been demonstrated in several therapeutic areas.[7-11] However, there is a lack of both comprehensive overviews on sex- and gender differences of drug ~~utilisation~~ use in entire populations and especially studies analysing the rationale behind the observed differences. Variations in morbidity may explain some differences, whereas other differences may indicate inequities and under- or overuse of certain drugs in men or women.

WHO defines "drug utilisation" as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the medical, social, and economic consequences".[12] Drug utilisation data can be derived from different levels in the medication use process; sales

data from the manufacturers to wholesalers, the dispensing data at pharmacies, or patient consumption surveys.[13 14] The use of dispensed prescriptions as a measure of drug exposure has many advantages since it eliminates recall bias and improves the accuracy of the information on the drug use.[13 15] In 2005, a national registry on dispensed drugs to the entre Swedish population was established.[16] It contains complete data (>99 % coverage) with unique identifiers of all prescribed drugs dispensed to the entire Swedish population of 9.3 million inhabitants, and may offer a good opportunity to study sex and gender differences in drug use.

The aim of this study was to describe and analyse differences in prevalence and incidence between men and woman of drugs dispensed ~~utilisation among~~to ~~men and women in~~ the Swedish population. The findings may subsequently be used to plan future studies to address differences suggesting inequity in treatment approaches.

Methods

This was a cross-sectional study analysing sex differences in prevalence and incidence of drugs dispensed ~~utilisation~~ in ambulatory care in Sweden in 2010, overall and within different pharmacological groups. Data were collected from the Swedish Prescribed Drug Register (SPDR)~~, which contains complete data (>99 % coverage) with unique identifiers of all prescribed drugs dispensed to the entire Swedish population of 9.3 million inhabitants~~.[16]

The period prevalence was defined as the proportion of the population in the country ~~purchasing~~ dispensed ≥1 prescription in 2010 and measured in number of patients exposed per 1000 inhabitants (PAT/TIN). Incidence was defined as the proportion of the population having at least one prescription dispensed in a pharmacy in 2010 after a one-year wash-out

period with no drug dispensed and was measured in number of patients per 1000 person-years (PAT/1000 PYs).

Pharmacological groups were selected by using the following procedure:

1. All 89 Anatomical Therapeutic Chemical (ATC) 2nd level groups with drugs available on the Swedish market[17 18] were identified.
2. In large ATC groups and ATC groups with drugs used for multiple heterogeneous indications, i.e. cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06), ophthalmologicals (S01), a subdivision was done to ATC 3rd or 4th level to attain a more clinically relevant description of the utilisation.
3. ATC groups with less than 75% of the total sales volume in the country purchased on prescription were excluded since sex distribution was not possible to collect for those purchased over-the-counter (OTC) or used in inpatient care. Volume was measured in the technical unit numbers of Defined Daily Doses (DDDs), except for eight pharmacological groups for which there were no DDDs assigned.[18] For these groups, packages were used as volume measure. Calculations of the proportion of the total volume dispensed as prescriptions in ambulatory care were based on aggregated volume data from all Swedish pharmacies.
4. For the identified ATC groups at various hierarchical levels, groups that were dispensed to less than 1% of the total Swedish population or dispensed to less than 0.4% of men or women, respectively, were excluded to avoid random variation due to small numbers.

Crude and age adjusted values were calculated. Age standardisation was performed by direct standardisation, where the Swedish population on 31 December 2009 (4 649 014 men and 4 691 668 women[19]) was used as the standard population. In the calculations, 5-year age groups were used. Differences between the sexes were calculated as a risk ratio (RR) of women/men with 95% confidence intervals (CI). All analyses were performed in Microsoft Excel 2007 and SAS ver. 9.2 (SAS Institute, Cary, NC) using descriptive statistical methods.

Results

In 2010, the total volume of drugs dispensed in Sweden was 5.8 billion Defined Daily Doses (DDD), corresponding to 1715 DDD/1000 inhabitants daily. The total expenditures were 35.6 billion Swedish Kronor (SEK) (100 SEK = 8.96 GBP, September 2012). Drugs prescribed in ambulatory care, and thus included in the study, accounted for 88 % of the total volume and 72 % of the total expenditures on drugs in the country.

In all, 2.8 million men (59%) and 3.6 million women (76%), were dispensed at least one prescribed drug during 2010. The older the patient, the higher the likelihood was of being dispensed drugs. Women were in general dispensed more prescription drugs in all age groups except among children under the age of 10, even when hormonal contraceptives were excluded (Table 1).

Crude sex differences in prevalence were found in 48 of the 50 pharmacological ATC groups included (Figure 1, Table 2). After age adjustment, sex differences remained in 48 ATC groups. Concerning~~For~~ drugs for glaucoma (S01E) and endocrine drugs (L02), the sex differences disappeared after age adjustment, while the opposite was seen for angiotensin receptor blockers (ARBs) (C09C+D) and calcium channel blockers (C08), that were more common ~~with a slightly higher utilisation~~ in men after age adjustment. Beta blocking agents (C07) and cardiac glycosides (C01A) were more common in women before age adjustment, but were found to be more common in men after adjustment. The large differences in drugs for treatment of bone diseases such as osteoporosis (M05), thyroid therapy (H03), mineral supplements (A12) and anti-dementia drugs (N06D) diminished after age adjustment, even though they still were more common ~~higher utilisation~~ in women after adjustment~~remained~~ (Table 2).

The pharmacological groups with the largest relative differences ~~with higher utilisation~~more commonly being dispensed to ~~in~~ women were antimycotics for systemic use (RR 6.6), drugs for osteoporosis (RR 4.9) and thyroid therapy (RR 4.5), while ~~the utilisation was higher in~~a larger proportion of men ~~for~~ were dispensed anti-gout preparations (RR 0.4), psychostimulants (0.6) and ACE-inhibitors (RR 0.7) (Figure 2).

The largest sex difference in absolute numbers was found for systemic antibacterials (J01) that were more common in women, 265.5 PAT/1000 women and 191.3 PAT/1000 men, respectively. This was followed by thyroid therapy (H03), 65.7 PAT/1000 women and 13.1 PAT/1000 men, and antidepressants (N06A), 106.6 PAT/1000 women and 55.4 PAT/1000 men.

The incidence showed a similar pattern as the prevalence (Table 3). However, the sex differences were substantially higher for endocrine therapy (L02) and urinary antispasmodic agents (G04BD). Before age adjustment, 40 pharmacological groups were more frequently dispensed to women and eight groups to men. After age adjustment, sex differences remained in 36 and 11 ATC-groups for women and men, respectively. In only one pharmacological group, drugs for treatment of bone diseases (M05), the sex difference diminished substantially after age adjustment.

Discussion

This study of all dispensed prescription drugs in Sweden shows substantial differences ~~in drug utilization~~ between men and women. It is obvious that some of these differences may be explained by variations in disease prevalence, severity of disease, pathophysiology,

diagnostics and treatment response or by other biologic differences such as those induced by pregnancy and/or lactation. However, it is also evident that other differences lack a rational medical explanation.

Throughout their lifespan, women have more contact with the health care system[20-22], which may provide them with an extra opportunity for detection of disease and receiving prescriptions. In the pre-menopausal years, a woman's need for contraceptives, pregnancy and childbirth and, in the peri- and postmenopausal period, screening programs for breast and cervical cancers and gynecological disorders require health care consultations.[22] Also, chronic disabling diseases associated with a chronic need for medication, such as musculoskeletal disorders, are more common in women than men.[20] From a gender perspective, studies have shown that men are less prone to seek preventive health care.[21]

Some differences between the sexes ~~were~~ are expected. The higher proportion~~utilisation~~ of women dispensed antimycotics ~~in women~~ could partly be explained by gynecological infections such as vaginitis. Also, the 4.5 times higher ~~utilisation of~~proportion of dispensed thyroid therapy corresponds to a four times higher prevalence of impaired thyroid function in women.[23] The sex difference in ~~utilisation~~ the proportion of dispensed~~of~~ drugs for migraine could be explained by a two to three times higher prevalence of migraine among women.[24] Men were dispensed more psychostimulants, corresponding to a higher prevalence of ADHD[25] and autism[26].

The~~A~~ largest sex difference ~~with a higher~~in absolute numbers was observed for ~~utilisation of~~ antibiotics, more commonly dispensed to ~~was observed in~~ women. A common reason for prescribing antibiotics in primary care is urinary tract infection (UTI), which is more prevalent in women.[27] An over diagnosis of this condition in women has, however, been

reported, which could potentially explain some of the higher ~~utilisation~~ number of~~in~~ women dispensed these drugs.[28] Women were dispensed more anti-obesity drugs than men in spite of obesity being more common in men.[29 30] Also, more women than men undergo obesity surgery.[31] There are reasons to believe that the sociocultural pressure ~~for women~~ to be slim is higher ~~than~~ for women and studies have shown that women are more dissatisfied with their weight and their body than men.[32 33] This~~which~~ could explain ~~this~~ the prescription pattern. ~~However, this needs substantiation before any definitive statements can be made.~~

In the cardiovascular field, several differences in ~~utilisation~~ dispensing of prescribed drugs were found. ACE inhibitors, primarily used for the treatment of heart failure and hypertension with the same prevalence in both sexes, were ~~utilised by~~more commonly dispensed to men ~~to a larger extent~~. This may be due to the higher frequency of coughing as an adverse event in women.[34] However, the alternative treatment ARB was dispensed to women and men to the same extent. Our findings may therefore indicate an under-use of renin-angiotensin-agents in women. Lipid lowering drugs were also dispensed more frequently ~~among~~ to men. The higher ~~utilisation~~ proportion in men may be explained by the higher prevalence of ischemic heart disease (IHD). However, studies have shown that these drugs are under-used for secondary prevention in women.[35-38] Reasons for this could be that women suffer more from myalgia as an adverse reaction[39] but also that women are older and have more co-morbidity when suffering from cardiovascular disease, thus receive less intensive secondary preventive medication.

Men were dispensed more anticoagulants. The most common indication for anticoagulants is atrial fibrillation, a condition more commonly found in men but carrying a higher risk of fatal complications like embolic stroke, for women.[40] Underuse of anticoagulants in women with atrial fibrillation has been shown in earlier studies.[37 38 41-44] Men were also dispensed anti-

arrhythmic drugs to a higher degree than women. This may be appropriate as women have a higher risk of the fatal arrhythmia "torsade de pointe-ventricular tachycardia" induced by some anti-arrhythmics like sotalol and quinidine.[45]

The main strength of this study is the complete coverage of all dispensed prescription drugs to the entire Swedish population. This provides a population-based overview of drug ~~utilisation~~ use difficult to acquire in many other health systems.[15] Although, it is important to recognise that filling a prescription does not necessarily imply that the drugs are taken, we have no reason to believe that misclassification of drug use should be more prevalent in one sex. Furthermore, data on dispensed drugs is closer to the actual ~~consumption~~ intake than data on prescribed drugs, and it is free from recall bias common in patient reported data.[46] The most important limitation is the lack of information on patient characteristics and clinical data to assess the rationale behind the observed differences. ~~Furthermore~~Moreover, it is important to ~~emphasize~~ emphasise that gender differences may only be ~~hypothesized~~ hypothesised from these data.

In conclusion, in this large study we found substantial differences in drugs ~~utilisation~~ dispensed to~~between~~ men and women. In an attempt to explain these sex differences we searched the literature. Some sex disparities could be explained by differences in prevalence of disease or frequency of adverse reactions. Less medically justified explanations were also identified such as overestimation of risk vs. benefit in women compared to men. We also found suggestions that gender aspects such as societal acceptance of overweight in women compared to men may be involved. More research and a greater awareness of the influence of sex- and gender in health and disease are needed to ensure rational drug use in both men and women.

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Contributors: KSG proposed the study. All authors developed the study design. DL conducted the analyses. All authors contributed to interpreting the data and drafting the manuscript.

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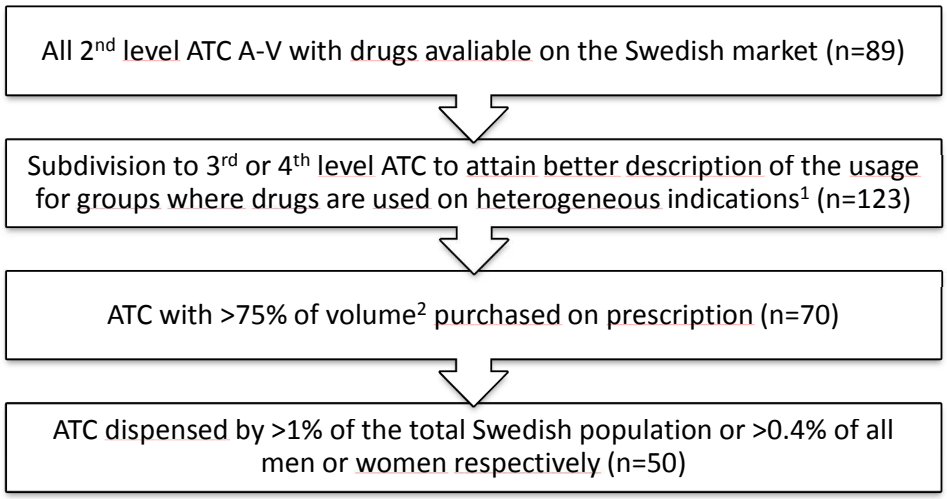
Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the regional Ethics Committee at Karolinska Institutet, Sweden. Ref. no. 2010/788-31/5.

Data sharing: Proposals for data sharing should be sent to the corresponding author.

Figure 1. Flow chart showing the selection of pharmacological groups included in the specific analyses on sex- and gender differences in different therapeutic areas.



[1] Cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06) and ophthalmologicals (S01)

[2] Volume was measured in Defined Daily Doses (DDDs), except for eight ATC groups without any assigned DDD values where packages were used instead.

Figure 2. Pharmacological groups with the highest age adjusted relative differences in prevalence 2010.

ATC	Pharmacological group	PAT/TIN	
		Men	Women
J02	Antimycotics for systemic use	2.8	18.9
M05	Drugs for treatment of bone diseases	3.2	19.3
H03	Thyroid therapy	13.1	65.7
N02C	Antimigraine preparations	5.0	17.2
A12	Mineral supplements	16.2	57.3
A08	Antiobesity preparations	1.6	4.1
J05	Antivirals for systemic use	7.9	14.8
P01	Antiprotozoals	11.0	20.6
N06A	Antidepressants	55.4	106.6
H01	Pituitary and hypothalamic hormones	2.5	4.1
C09C+D	Angiotensin II antagonists and comb.	45.2	46.6
C08	Calcium channel blockers	60.8	59.6
C01A	Cardiac glycosides	6.0	6.8
C10	Lipid modifying agents	98.0	81.1
C01D	Vasodilators used in cardiac diseases	24.9	23.6
B01	Antithrombotic agents	109.8	97.7
A10	Drugs used in diabetes	45.3	34.5
C09A+B	ACE inhibitors and combinations	78.1	60.9
N06B	Psychostimulants	6.9	4.1
M04	Antigout preparations	12.2	5.9

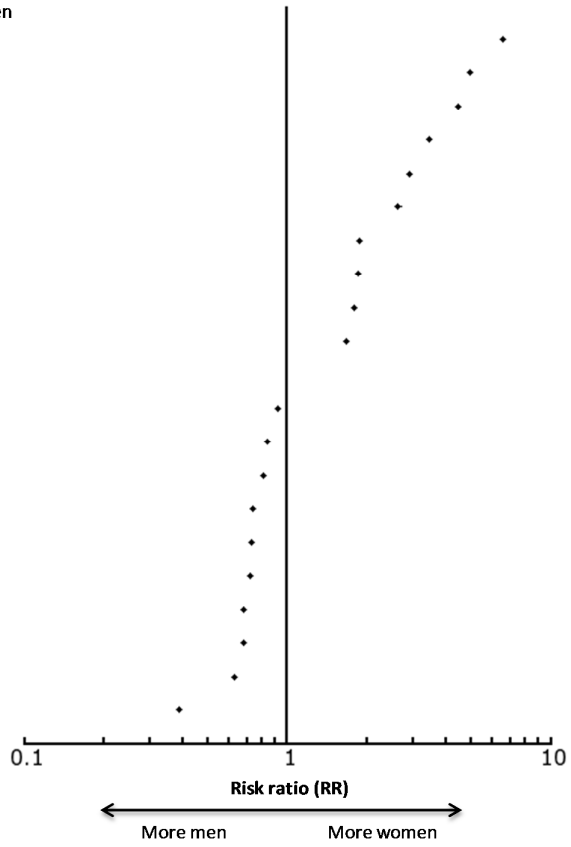


Table 1. Proportions of the Swedish population dispensed at least one prescribed drug in 2010, by age and sex.

Age group	Men (%)	Women (%)	Women excl. hormonal contraceptives (G03A) (%)
0- 4	68	64	64
5- 9	45	43	43
10-14	39	45	44
15-19	42	77	62
20-24	39	77	60
25-29	42	74	62
30-34	46	73	65
35-39	50	73	66
40-44	53	73	67
45-49	58	74	71
50-54	64	78	77
55-59	72	82	82
60-64	79	85	85
65-69	84	88	88
70-74	89	92	92
75-79	93	94	94
80-84	95	96	96
85-89	96	96	96
90 +	97	99	99
Total	*59*	*76*	*71*

Table II. Sex differences in prevalence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/TIN = number of patients (men or women) per 1000 individuals. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/TIN		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.75	18.90	6.87 (6.74-7.00)	6.56 (6.44-6.68)
M05	Drugs for treatment of bone diseases	3.19	19.28	6.04 (5.94-6.14)	4.95 (4.87-5.03)
H03	Thyroid therapy	13.12	65.67	5.00 (4.96-5.05)	4.46 (4.42-4.50)
N02C	Antimigraine Preparations	5.03	17.24	3.43 (3.38-3.48)	3.44 (3.39-3.49)
A12	Mineral supplements	16.19	57.29	3.54 (3.51-3.57)	2.90 (2.88-2.92)
A08	Antiobesity preparations	1.59	4.13	2.60 (2.53-2.67)	2.62 (2.55-2.69)
J05	Antivirals for systemic use	7.85	14.79	1.88 (1.86-1.91)	1.86 (1.84-1.89)
P01	Antiprotozoals	11.00	20.55	1.87 (1.85-1.89)	1.85 (1.83-1.87)
N06A	Antidepressants	55.35	106.60	1.93 (1.92-1.93)	1.79 (1.78-1.80)
H01	Pituitary and hypothalamic hormones and analogues	2.46	4.08	1.66 (1.62-1.70)	1.66 (1.63-1.70)
N05B	Anxiolytics	39.39	70.01	1.78 (1.77-1.79)	1.60 (1.59-1.61)
N05C	Hypnotics and sedatives	58.35	103.83	1.78 (1.77-1.79)	1.56 (1.56-1.57)
M03	Muscle relaxants	6.38	9.98	1.56 (1.54-1.59)	1.53 (1.51-1.56)
B03	Antianemic preparations	40.35	73.24	1.82 (1.81-1.83)	1.48 (1.47-1.49)
J01	Antibacterials for systemic use	191.26	265.58	1.39 (1.39-1.39)	1.36 (1.36-1.36)
L04	Immunosuppressants	7.32	10.05	1.37 (1.35-1.39)	1.33 (1.31-1.35)
G04BD	Urinary antispasmodics	6.12	9.61	1.57 (1.55-1.60)	1.33 (1.31-1.35)
A02	Drugs for acid related disorders	70.08	101.87	1.45 (1.45-1.46)	1.31 (1.31-1.32)
H02	Corticosteroids for systemic use	37.17	51.98	1.40 (1.39-1.41)	1.30 (1.30-1.31)
S01B	Anti-inflammatory agents	12.72	18.95	1.49 (1.47-1.50)	1.30 (1.29-1.31)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	13.77	19.35	1.40 (1.39-1.42)	1.29 (1.28-1.30)
N02A	Opioids	66.90	92.97	1.39 (1.38-1.40)	1.27 (1.27-1.28)
C03	Diuretics	59.48	92.83	1.56 (1.55-1.57)	1.24 (1.24-1.25)
S02	Otologicals	4.54	5.71	1.26 (1.24-1.28)	1.23 (1.21-1.25)
R03	Drugs for obstructive airway diseases	71.79	88.80	1.24 (1.23-1.24)	1.20 (1.20-1.21)
S03	Ophthalmological and otological preparations	23.31	28.38	1.22 (1.21-1.23)	1.18 (1.17-1.19)

N03	Antiepileptics	18.22	22.08	1.21 (1.20-1.22)	1.15 (1.14-1.16)
N05A	Antipsychotics	13.59	16.51	1.21 (1.20-1.23)	1.11 (1.09-1.12)
N06D	Anti-dementia drugs	3.38	5.41	1.60 (1.57-1.63)	1.10 (1.07-1.12)
N04	Anti-parkinson drugs	6.83	8.49	1.24 (1.22-1.26)	1.06 (1.05-1.08)
S01E	Antiglaucoma preparations and miotics	13.57	18.49	1.36 (1.35-1.38)	1.02 (1.01-1.03)
L02	Endocrine therapy	6.34	7.60	1.20 (1.18-1.22)	0.96 (0.95-0.97)
C07	Beta blocking agents	97.82	107.57	1.10 (1.10-1.10)	0.94 (0.93-0.94)
C09C+D	Angiotensin II antagonists and combinations	45.16	46.56	1.03 (1.02-1.04)	0.91 (0.91-0.92)
C08	Calcium channel blockers	60.84	59.61	0.98 (0.97-0.98)	0.84 (0.84-0.84)
C01A	Cardiac glycosides	6.01	6.83	1.14 (1.12-1.16)	0.81 (0.79-0.82)
C10	Lipid modifying agents	98.03	81.05	0.83 (0.82-0.83)	0.74 (0.73-0.74)
C01D	Vasodilators used in cardiac diseases	24.94	23.61	0.95 (0.94-0.95)	0.73 (0.72-0.73)
B01	Antithrombotic agents	109.81	97.68	0.89 (0.89-0.89)	0.72 (0.72-0.73)
A10	Drugs used in diabetes	45.27	34.48	0.76 (0.76-0.77)	0.68 (0.68-0.69)
C09A+B	ACE-inhibitors and combinations	78.14	60.90	0.78 (0.78-0.78)	0.68 (0.67-0.68)
N06B	Psychostimulants	6.94	4.11	0.59 (0.58-0.60)	0.62 (0.61-0.64)
M04	Antigout preparations	12.24	5.91	0.48 (0.48-0.49)	0.38 (0.38-0.39)

*The following pharmacological groups are not presented in the table due to sex-specific indications; G02 Other gynecologicals (dispensed to 9.79 PAT/1000 women and 0.20 PAT/1000 men), G03A Hormonal contraceptives (dispensed to 132.05 PAT/1000 women and 0.08 PAT/1000 men), G03C Estrogens (dispensed to 69.62 PAT/1000 women and 0.08 PAT/1000 men), G03D Progestogens (dispensed to 15.90 PAT/1000 women and 0.03 PAT/1000 men), G03F Progestogens and estrogens in combination (dispensed to 12.26 PAT/1000 women and 0.00 PAT/1000 men), G04C Drugs used in benign prostatic hypertrophy (dispensed to 0.25 PAT/1000 women and 26.23 PAT/1000 men) and G04BE Drugs used in erectile dysfunction (dispensed to 25.38 PAT/1000 men and 0.07 PAT/1000 women).

Table III. Sex differences in incidence of drug therapy in Sweden 2010 by pharmacological group.

Crude and age adjusted relative differences for included ATC groups.* The relative differences were calculated with women as the numerator and men as the denominator. Table is sorted starting with the group with the largest age adjusted sex difference. PAT/1000 PYs = number of patients (men or women) per 1000 patient-years. N = 4 649 014 men and 4 691 668 women.

ATC	Pharmacological group	PAT/1000 PYs		RR (95 C.I.)	Age adj. RR (95 C.I.)
		Men	Women	Women/Men	Women/Men
J02	Antimycotics for systemic use	2.28	13.23	5.80 (5.68-5.92)	5.49 (5.38-5.60)
H03	Thyroid therapy	1.55	5.77	3.72 (3.62-3.81)	3.49 (3.40-3.58)
M05	Drugs for treatment of bone diseases	0.97	3.98	4.11 (3.98-4.24)	3.49 (3.38-3.60)
N02C	Antimigraine Preparations	1.89	4.99	2.64 (2.57-2.70)	2.67 (2.61-2.74)
A08	Antiobesity preparations	0.55	1.41	2.57 (2.45-2.69)	2.60 (2.48-2.72)
H01	Pituitary and hypothalamic hormones and analogues	0.99	2.45	2.47 (2.38-2.55)	2.48 (2.40-2.57)
A12	Mineral supplements	5.82	14.85	2.55 (2.52-2.59)	2.21 (2.18-2.24)
J05	Antivirals for systemic use	4.60	8.53	1.85 (1.82-1.89)	1.80 (1.77-1.83)
P01	Antiprotozoals	9.38	16.83	1.80 (1.77-1.82)	1.79 (1.76-1.81)
B03	Antianemic preparations	12.28	23.72	1.93 (1.91-1.95)	1.70 (1.68-1.72)
N06A	Antidepressants	15.35	24.71	1.61 (1.59-1.62)	1.52 (1.51-1.54)
L02	Endocrine therapy	1.37	2.43	1.78 (1.73-1.84)	1.52 (1.48-1.56)
N05B	Anxiolytics	17.90	28.41	1.59 (1.57-1.60)	1.47 (1.46-1.48)
M03	Muscle relaxants	4.50	6.67	1.48 (1.46-1.51)	1.46 (1.44-1.49)
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	6.68	10.27	1.39 (1.37-1.41)	1.39 (1.37-1.41)
A02	Drugs for acid related disorders	25.47	37.35	1.47 (1.46-1.48)	1.38 (1.37-1.39)
N05C	Hypnotics and sedatives	18.90	26.94	1.43 (1.41-1.44)	1.32 (1.31-1.34)
S01B	Anti-inflammatory agents	9.27	13.71	1.48 (1.46-1.50)	1.29 (1.27-1.31)
H02	Corticosteroids for systemic use	21.36	28.28	1.32 (1.31-1.33)	1.27 (1.26-1.28)
N03	Antiepileptics	4.76	6.29	1.32 (1.30-1.35)	1.25 (1.22-1.27)
L04	Immunosuppressants	1.43	1.80	1.26 (1.22-1.30)	1.23 (1.20-1.27)
J01	Antibacterials for systemic use	126.14	153.73	1.22 (1.21-1.22)	1.21 (1.20-1.21)
R03	Drugs for obstructive airway diseases	27.19	32.11	1.18 (1.17-1.19)	1.19 (1.18-1.20)

N04	Anti-parkinson drugs	1.67	2.26	1.35 (1.31-1.39)	1.19 (1.15-1.22)
S02	Otologicals	3.39	4.04	1.19 (1.17-1.22)	1.17 (1.14-1.19)
N02A	Opioids	39.55	48.30	1.22 (1.21-1.23)	1.14 (1.14-1.15)
C03	Diuretics	10.63	14.35	1.35 (1.33-1.37)	1.14 (1.13-1.15)
S03	Ophthalmological and otological preparations	18.43	21.41	1.16 (1.15-1.17)	1.14 (1.13-1.15)
G04BD	Urinary antispasmodics	2.63	3.33	1.27 (1.24-1.30)	1.10 (1.08-1.13)
N05A	Antipsychotics	3.27	4.03	1.23 (1.21-1.26)	1.07 (1.05-1.10)
N06D	Anti-dementia drugs	0.91	1.38	1.52 (1.46-1.58)	1.07 (1.03-1.11)
B01	Antithrombotic agents	15.05	17.48	1.16. (1.15-1.7)	1.05 (1.04-1.06)
C07	Beta blocking agents	12.16	13.61	1.12 (1.11-1.13)	1.02 (1.01-1.03)
S01E	Antiglaucoma preparations and miotics	1.90	2.15	1.13 (1.10-1.16)	0.96 (0.93-0.98)
C09C+D	Angiotensin II antagonists and combinations	6.18	6.42	1.04 (1.02-1.05)	0.95 (0.93-0.96)
C08	Calcium channel blockers	10.35	10.72	1.04 (1.02-1.05)	0.93 (0.92-0.94)
C01A	Cardiac glycosides	1.09	1.24	1.14 (1.10-1.18)	0.86 (0.82-0.89)
C09A+B	ACE-inhibitors and combinations	14.28	13.11	0.92 (0.91-0.93)	0.83 (0.82-0.84)
C10	Lipid modifying agents	13.01	11.28	0.87 (0.86-0.88)	0.81 (0.80-0.82)
A10	Drugs used in diabetes	4.83	3.79	0.79 (0.77-0.80)	0.73 (0.72-0.75)
N06B	Psychostimulants	2.36	1.57	0.67 (0.65-0.69)	0.70 (0.68-0.72)
C01D	Vasodilators used in cardiac diseases	8.34	6.93	0.83 (0.82-0.84)	0.69 (0.68-0.70)
M04	Antigout preparations	2.71	1.44	0.53 (0.51-0.55)	0.44 (0.42-0.45)

*The following pharmacological groups were excluded from the table due to sex-specific indications; G02 Other gynecologicals (dispensed to 5.33 PAT/1000 PYs in women and 0.03 PAT/1000 PYs in men), G03A Hormonal contraceptives (dispensed to 42.09 PAT/1000 PYs in women and 0.04 PAT/1000 PYs in men), G03C Estrogens (dispensed to 16.44 PAT/1000 PYs in women and 0.03 PAT/1000 PYs in men), G03D Progestogens (dispensed to 11.20 PAT/1000 PYs in women and 0.01 PAT/1000 PYs in men), G03F Progestogens and estrogens in combination (dispensed to 2.56 PAT/1000 PYs in women and 0.00 PAT/1000 PYs in men), G04C Drugs used in benign prostatic hypertrophy (dispensed to 0.20 PAT/1000 PYs in women and 7.34 PAT/1000 PYs in men) and G04BE Drugs used in erectile dysfunction (dispensed to 0.03 PAT/1000 PYs in women and 10.16 PAT/1000 PYs in men).

Article Summary

Article focus

- To use drug dispensing data to analyse drug utilisation in men and women in a whole country
- To identify areas of potential discrepancies in drugs ~~utilisation patterns~~dispensed to ~~between~~ men and women
- To review existing literature for explanations for differences in drug ~~utilisation~~ use between men and women
- To raise awareness about differences in drug ~~utilisation~~ use between men and women which may not be rational

Key messages'

- Differences in ~~drug utilisation between~~ men and women in ~~both~~ the prevalence and incidence of dispensed drugs were found in Sweden overall, and for 48 of 50 pharmacological groups.
- Many sex differences ~~in drug utilisation~~found in our study may be explained by sex differences in morbidity or biology. Other differences are hard to explain on medical grounds and may indicate unequal treatment.
- There are few studies analysing the rational of the observed sex differences.

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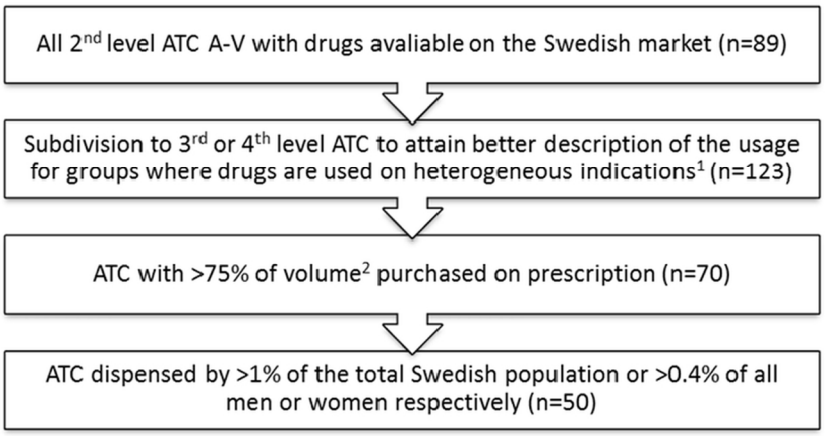
Figure 1. Flow chart showing the selection of pharmacological groups included in the specific analyses on sex- and gender differences in different therapeutic areas.



[1] Cardiac therapy (C01), agents acting on the renin-angiotensin system (C09), sex hormones (G03), urologicals (G04), analgesics (N02), psycholeptics (N05), psychoanaleptics (N06) and ophthalmologicals (S01)

[2] Volume was measured in Defined Daily Doses (DDDs), except for eight ATC groups without any assigned DDD values where packages were used instead.

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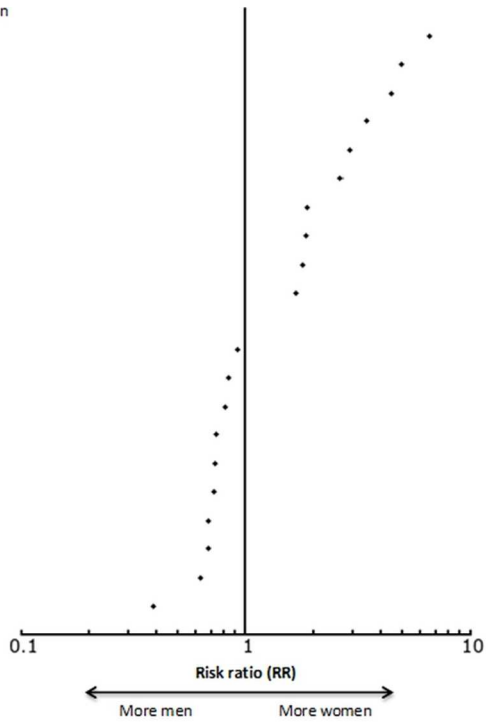
Figure 2. Pharmacological groups with the highest age adjusted relative differences in prevalence 2010.

ATC	Pharmacological group	PAT/TIN	
		Men	Women
J02	Antimycotics for systemic use	2.8	18.9
M05	Drugs for treatment of bone diseases	3.2	19.3
H03	Thyroid therapy	13.1	65.7
N02C	Antimigraine preparations	5.0	17.2
A12	Mineral supplements	16.2	57.3
A08	Antiobesity preparations	1.6	4.1
J05	Antivirals for systemic use	7.9	14.8
P01	Antiprotozoals	11.0	20.6
N06A	Antidepressants	55.4	106.6
H01	Pituitary and hypothalamic hormones	2.5	4.1
C09C+D	Angiotensin II antagonists and comb.	45.2	46.6
C08	Calcium channel blockers	60.8	59.6
C01A	Cardiac glycosides	6.0	6.8
C10	Lipid modifying agents	98.0	81.1
C01D	Vasodilators used in cardiac diseases	24.9	23.6
B01	Antithrombotic agents	109.8	97.7
A10	Drugs used in diabetes	45.3	34.5
C09A+B	ACE inhibitors and combinations	78.1	60.9
N06B	Psychostimulants	6.9	4.1
M04	Antigout preparations	12.2	5.9



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